19	FEDERAL REPUBLIC OF GERMANY	12	OLS	51	Int. Cl[6]:
		30	DE 43 38 770 A1		**C 07 D 209/42** C 07 D 403/04 C 07 D 403/06 C 07 D 403/12 C 07 D 401/06 C 07 D 209/18 A 61 K 31/405 A 61 K 31/41 C 12 N 9/99 // C07D 521/00 (C07D 209/42, 257:04, 213:24) C12N 9/16
	GERMAN PATENT OFFICE	21 22 43	File number: P 43 38 770.5 Application date: 11/12/93 Disclosure date: 5/18/95		

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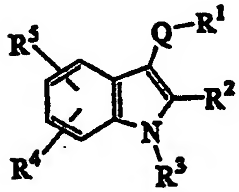
Examination request according to § 44 PatG has been issued.

54 Indole-2-alkane acids and their derivatives as inhibitors of phospholipase A_2

57 The invention relates to Indole-2-alkane acids and their derivatives of the general formula:



wherein
R^1 indicates an alkyl, alkenyl, alkinyl, aryl, arylalkyl, arylalkenyl or arylalkinyl group,
R^2 indicates an alkane acid, alkene acid or a 1H or 2H-Tetrazol-5-yl, 1H or 2H-Tetrazol-5-yl-alkyl or 1H or 2H-Tetrazol-5-yl-alkenyl group,
R^3 indicates an alkyl, alkenyl, alkinyl, aryl, arylalkyl, arylalkenyl or arylalkinyl group and/or a hydroxy, thiol, amino, acyloxy, acylthio or acylamino substituted alkyl, alkenyl, alkinyl, aryl, arylalkyl, arylalkenyl or arylalkinyl group;
R4 and R5, independently of each other, stand for halogen, alkyl, alkoxy, nitro, cyano, etc.,
Q indicates a carbonyl, methylene, CHNHC-OR^a group, whereby R^a can stand for an alkyl, alkenyl, alkinyl, aryl, arylalkyl, arylalkenyl or arylalkinyl group,
and their use in pharmaceuticals. The compounds according to the invention are potent inhibitors of phospholipase A_2 and thus can be used to prevent and treat diseases that are cause or partially caused by elevated activity of phospholipase A_2, like inflammation, allergies, asthma, psoriasis and endotoxic shock.

The following information was taken from the documents submitted by the applicant

Description

The invention relates to indole-2-alkane acids and their derivatives, which inhibit the enzyme phospholipase A_2. The compounds are suitable as medications for prevention and treatment of diseases that are caused or partially caused by increased activity of this enzyme, e.g. inflammation, allergies, asthma, psoriasis and endotoxic shock. The invention also relates to methods for preparing these compounds and pharmaceutical agents that contain these compounds.

Background of the Invention

It is known that phospholipase A_2 hydrolytically cleaves the ester bond in the 2-position of membrane phospholipids, whereby free fatty acids, mainly arachidonic acid, and lyso-phospholipids develop.

The released arachidonic acid is metabolized by way of the cyclooxygenase pathway to prostaglandins and thromboxanes and by way of the lipoxygenase pathway to leukotrienes and other hydroxylated fatty acids. The prostaglandins participate significantly in the development of pain and fever, as well as inflammatory reactions. Leukotrienes are important mediators in inflammatory processes and in anaphylactic and allergic events (Forth et al., General and Special Pharmacology and Toxicology, BI Wissenschaftsverlag, Mannheim, Vienna, Zurich 1987).

The lyso-phospholipids formed by phospholipase A_2 have cell-damaging properties. Lyso-phosphatidylserine leads to the release of histamine that is involved in allergic processes (Moreno et al., Agents Actions 1992, 36, 258). In addition, lyso-phosphatidylcholine is metabolized to platelet-activating factor (PAF) that is also an important mediator, e.g. in inflammation.

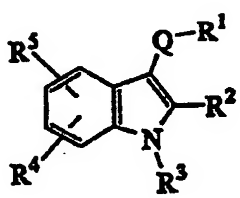
Since phospholipase A_2 represents the key enzyme for the formation of the named patho-physiologically significant mediators, these mediator effects can be prevented by inhibition of the enzyme.

The patho-physiological significance of phospholipase A_2 is also seen in that its activity is clearly elevated in various disease conditions: for example, there are high phospholipase A_2 activities in the synovial fluid of patients with rheumatoid arthritis (Vadas et al., Life Sci. 1985, 36, 579), in the serum of patients with endotoxic shock (Vadas, J. Lab. Clin. Med. 1984, 104, 873) or pancreatitis (Nevalainer, Scand. J. Gastroent. 1980, 15, 641) and in the epidermis of patients with psoriasis (Forster et al., Br. J. Derm. 1985, 112, 135) (see also Wong et al., Adv. Exp. Med. Biol. 1990, Vol. 275, Phospholipase A_2: Role and Function in Inflammation, Plenum Press, New York).

Object of the Invention

It has now been found that certain indole compounds are potent phospholipase A_2 inhibitors and thus can be used for prevention and treatment of diseases that are caused or partially caused by an elevated activity of this enzyme, e.g. inflammation, allergies, asthma, psoriasis and endotoxic shock.

Therefore, the object of the invention is indole compounds of the general formula:



wherein
R^1 stands for X, aryl or –X-Aryl, whereby X is a C_1-C_{19}-alkyl and/or C_2-C_{19}-alkenyl or alkinyl group that may be interrupted by an oxygen heteroatom, and aryl indicates an aryl group or an aryl group substituted with the radicals R^6 and R^7;
R^2 stands for –COOH, -Y-COOH, -Tz or –Y-Tz, whereby Y indicates a C_1-C_8-alkyl and/or C_2-C_8-alkenyl group that may be interrupted by an oxygen heteroatom and Tz indicates 1H- or 2H-tetrazol-5-yl;
R^3 stands for a hydrogen atom; for a C_1-C_{20}-alkyl and/or C_2-C_{20}-alkenyl or alkinyl group that may be interrupted by an oxygen heteroatom; for an aryl group or an aryl group substituted with the radicals R^8 and R^9; for –Z-aryl, whereby Z indicates a C_1-C_{20}-alkyl and/or C_2-C_{20}-alkenyl or alkinyl group that may be interrupted by an oxygen heteroatom and aryl indicates an aryl group or an aryl group substituted with the radicals R^8 and R^9; for –Z-OR^{16}, -Z-SR^{16}or –Z-NHR^{16}, whereby Z indicates a C_2-C_{20} alkyl and/or C_2-C_{20}-alkenyl or alkinyl group that may be interrupted by an oxygen heteroatom;
Q stands for CO, CH_2 and $CHNHCOR^{10}$, whereby R^{10} stands for W, aryl or –W-aryl and W can be a C_1-C_{19}-alkyl and/or C_2-C_{19}-alkenyl or alkinyl group that may be interrupted by an oxygen heteroatom and aryl indicates an aryl group or an aryl group substituted with the radicals R^{11} and R^{12}; R^4, R^5, R^6, R^7, R^8, R^9, R^{11} and R^{12} are selected independently of each other from among:

1) Hydrogen;
2) C_1-C_{20}-alkyl group that may be interrupted by an oxygen heteroatom;
3) C_2-C_{20}-alkenyl group that may be interrupted by an oxygen heteroatom;
4) C_2-C_{20}-alkinyl group that may be interrupted by an oxygen heteroatom;
5) Halogen;
6) $-CF_3$;
7) $-CN$;
8) $-NO_2$;
9) $-OR^{13}$;
10) $-SR^{13}$;
11) $-COOR^{13}$;
12) $-COR^{14}$;
13) $-COCH_2OH$;
14) $-NHCOR^{13}$;
15) $-NR^{13}R^{13}$;
16) $-NHSO_2R^{15}$;
17) $-SOR^{13}$;
18) $-SO_2R^{13}$;
19) $-CONR^{13}R^{13}$;
20) $-SO_2NR^{13}R^{13}$;
21) $-OOCR^{14}$;
22) $-OOCNR^{13}R^{13}$;
23) $-OOCOR^{13}$;
24) $-(CH_2)_rOR^{16}$;
25) $-(CH_2)_rSR^{16}$;
26) $-(CH_2)_rNHR^{16}$;
27) $-(CH_2)_sR^{17}$;
28) Perhalo-C_1-C_6-alkenyl;

R^{13} indicates, independently of each other, hydrogen, a C_1-C_{20}-alkyl and/or C_2-C_{19}-alkenyl or alkinyl group that may be interrupted by an oxygen heteroatom or $-(CH_2)_tR^{17}$;
R^{14} indicates, independently of each other, R^{13}, $-CF_3$, $-(CH)_2)_uCOOH$ or $-(CH_2)_uCOOR^{19}$;
R^{15} indicates, independently of each other, R^{13} or CF_3;
R^{16} indicates, independently of each other, hydrogen or $-COR^{19}$;
R^{17} indicates, independently of each other, aryl, substituted with one or two R^{18} groups;
R^{18} indicates, independently of each other, hydrogen, halogen, C_1-C_{12}-alkyl, C_1-C_{12}-alkoxy, C_1-C_{12}-alkylthio, C_1-C_{12}-alkylsulfonyl, C_1-C_{12}-alkylcarbonyl, $-CF_3$, $-CN$ or NO_2;
R^{19} indicates, independently of each other, C_1-C_6-alkyl, benzyl or phenyl;
r is 1 to 20;
s and t, independently of each other, are 0 to 12;
u is 0 to 4.

The invention also comprises the pharmaceutically compatible salts and – in the case of carboxylic acid – also the esters of the compounds for use in pharmaceuticals.

The pharmaceutically compatible salts can be base addition salts. This includes salts of compounds with inorganic bases, like alkali hydroxides, earth alkali hydroxides or with organic bases, like mono, di or triethanolamine.

In particular, esters that are physiologically easy to hydrolyze are included in the esters of the compounds, for example alkyl, pivaloyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethylene ester.

The term "alkyl" comprises straight chain, branched or cyclic alkyl groups like methyl, ethyl, propyl, butyl, pentyl, neopentyl, undecyl, dodecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, cyclododecyl, etc.

The term "alkenyl" comprises straight chain, branched or cyclic alkenyl groups like ethenyl, propenyl, butenyl, decenyl, heptadecenyl, cyclohexyl, etc.

The term "alkinyl" comprises straight chain or branched alkinyl groups like ethinyl, propinyl, butinyl, decinyl, heptadecinyl, etc.

The term "cycloalkyl" indicates a hydrocarbon ring of 3 to 7 carbon atoms like cyclopropyl, cylopentyl, cyclohexyl, etc.

The term "alkoxy" comprises straight chain, branched or cyclic alkoxy groups like methoxy, ethoxy, propoxy, cyclohexyloxy, etc.

The term "alkylthio" comprises straight chain, branched or cyclic alkylthio groups like methylthio, ethylthio, propylthio, cycloheptylthio, etc.

Aryl preferably stands for naphthyl or pyridyl, and especially for phenyl.

The term "halogen atom" comprises a fluorine, chlorine, bromine or iodine atom and especially a fluorine or chlorine atom.

The compounds according to the invention have proven to be potent inhibitors of phospholipase A_2. Therefore, the compounds can be used as medications for prevention and treatment of diseases that are caused or partially caused by products and/or secondary products of these enzymes, for example to treat the range of rheumatic diseases and for prevention and

treatment of allergy-induced diseases. The compounds according to the invention thus represent, among other things, effective antiphlogistics, antipyretics, antiallergy agents and broncholytics and can be used for prophylaxis of thrombosis and for prophylaxis of anaphylactic shock as well as for treatment of determatological diseases like psoriasis, urticaria, acute and chronic exanthema of allergic or non-allergic origin.

The compounds according to the invention can be dispensed either as individual therapeutic active ingredients or as mixtures with other therapeutic active ingredients. They can be administered alone; however, generally they are administered in the form of pharmaceutical agents, i.e. as mixtures of active ingredients with suitable pharmaceutical carriers or diluents. The compounds or agents can be administered orally, parenterally, by inhalation or topically (including dermal, transdermal, buccal and sublingual administration).

The type of pharmaceutical preparation and the pharmaceutical carrier or diluent depends on the desired type of administration. For example, oral compounds can be available e.g. as tablets or capsules, including in delayed action form, and contain the usual excipients like binders (e.g. syrup, acacia, gelatin, sorbitol, gum tragacanth or polyvinylpyrrolidone), fillers (e.g. lactose, sugar, corn starch, calcium phosphate, sorbitol or glycine), lubricants (e.g. magnesium stearate, talcum, polyethylene glycol or silicon dioxide), disintegrating agents (e.g. starches) or wetting agents (e.g. sodium lauryl sulfate). Liquid oral preparations can be available in the form of aqueous or oily suspensions, solutions, emulsions, syrups, elixirs or sprays, etc., or can be available as dry powder for reconstitution with water or another suitable carrier. This type of liquid preparations can contain the usual additives, e.g. suspending agents, flavorings, diluents or emulsifiers. For parenteral administration, solutions or suspensions with the usual pharmaceutical carriers can be used. For administration by inhalation, the compounds can be available in aqueous or partially aqueous solution that can be used in the form of an aerosol. Preparations for topical application can e.g. be available as pharmaceutically compatible powders, lotions, salves, creams, gels or as therapeutic systems that contain the therapeutically effective quantities of the compounds according to the invention.

The required dosage depends on the form of pharmaceutical preparation used, on the type of application, the severity of symptoms and the specific subject (human or animal) that will be treated. The treatment is usually started with a dose that lies below the optimum dose. After that, the dose is increased until the optimum effect is achieved for the given conditions. In general, the compounds according to the invention are best administered in concentrations at which positive effects can be achieved without the occurrence of damaging or disadvantageous effects. They can be administered in a single dose or in several doses.

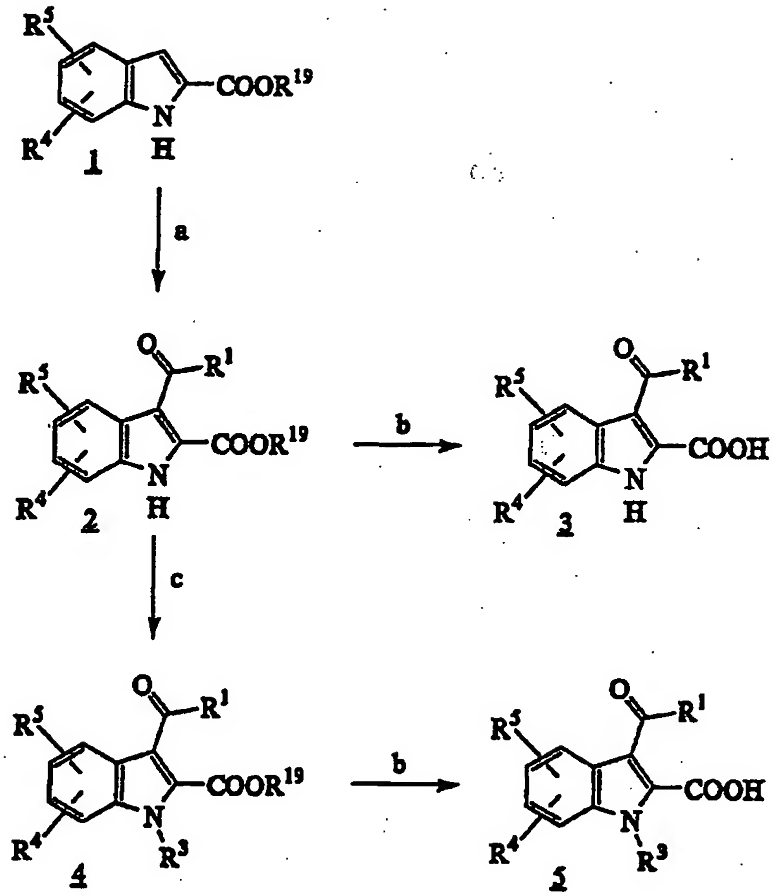
The effectiveness of the compounds according to the invention can be determined by the inhibition of phospholipase A_2. In order to do this, phospholipase A_2 is stimulated in intact bovine thrombocytes using Calcium Ionophore A23 187 and because of this, release of arachidonic acid is triggered from the membrane phospholipids. In order to prevent the metabolizing of the enzyme products of arachidonic acid by way of the cyclooxygenase pathway and the 12-lipoxygenase pathway, the dual cyclooxygenase/12-lipoxygenase inhibitor 5, 8, 11, 14-eicosatetraenoic acid is added. After purification using solid phase extraction, the arachidonic acid released is determined using RP-HPLC with UV detection. The inhibition of the enzyme by a test substance results from the ratio of the arachidonic acid quantities formed in the presence and/or and in the absence of the test substance. Further data on the test system will be given in the examples indicated below.

The compounds according to the invention can be prepared according to the following methods.

Method 1

Indole-2-carboxylic acid ester 1 can be reacted with carboxylic acids in the presence of trifluoroacetic acid anhydride and polyphosphoric acid, if necessary in a suitable solvent e.g. CH_2Cl_2 or nitrobenzene or with carboxylic acid chlorides according to Friedel-Crafts, to 3-Acylindole-2-carboxylic acid esters 2 (see Murakami et al., Chem. Pharm. Bull. 1985, 33, 4707-4716; Murakami et al., Heterocycles 1980, 14, 1939; Murakami et al., Heterocycles 1984, 22, 241-244; Murakami et al., Chem. Pharm. Bull. 1988, 36, 2023-2035; Tani et al., Chem. Pharm. Bull. 1990, 38, 3261-3267). These esters can be alkylated on indole nitrogen to the compounds 4. The N-alkylation is carried out, for example, as usual with the use of the corresponding alkyl halogenides in the presence of a base, e.g. alkali metal alcoholate, like potassium-t-butylate, in an inert solvent like DMSO or the like. The N-alkylation can also be carried out heterogeneously using toluenesulfonic acid alkyl esters or alkyl halogenides with the use of phase transfer catalysts in an organic solvent like ether, with the addition of powdered alkali hydroxide, like sodium hydroxide. The carboxylic acids 3 and/or 5 according to the invention can be produced from 2 and/or 4 by ester cleavage. The ester cleavage can be carried out hydrolytically, e.g. with alcoholic potassium hydroxide, or in the case of benzyl ester also hydrogenolytically, e.g. in THF with hydrogen in the presence of Pd/C. The latter method is mainly indicated if [appears to by typo in original, German word "dünn" that was used does not match word "dann" used in Method 3], in addition to this ester group, other hydrolysis-sensitive functions are contained in the compounds.

Method 1

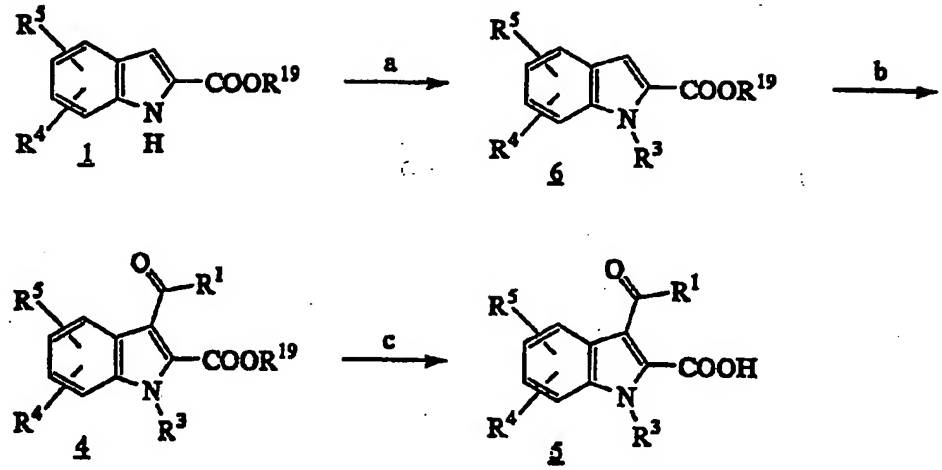


a) Carboxylic acid, trifluoroacetic acid anhydride, polyphosphoric acid, CH_2Cl_2; b) ethanolic potassium hydroxide <u>or</u> H_2, Pd/C, THF, if R^{19} = benzyl; (3) p-toluenesulfonic acid ester and/or alkyl halogenide, $(C_4H_9)_4NBr$, powdered NaOH, ether and/or ether/CH_2Cl_2 <u>or</u> alkyl halogenide, potassium-t-butylate, DMSO.

Method 2

Compounds of the formula 5 can also alternatively be prepared according to Method 2. In principle, the reactions correspond to the reactions in Method 1. However, in this case, the indole-2-carboxylic acid ester 1 is first N-alkylated and, only after that, acylated in position 3 of the indole.

Method 2

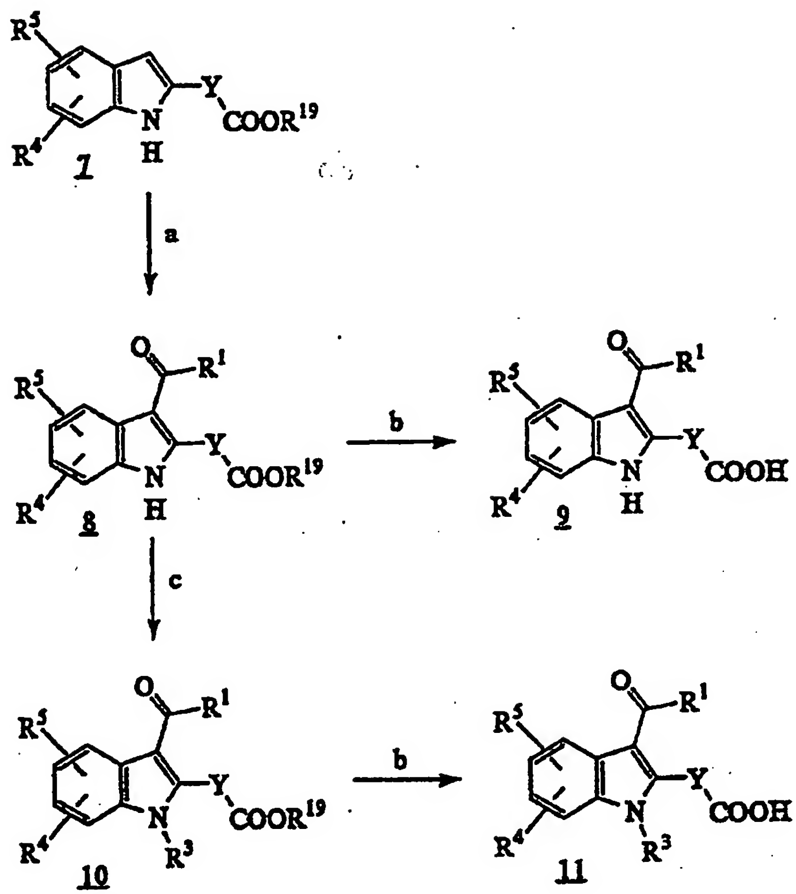


a) p-Toluenesulfonic acid ester and/or alkyl halogenide, $(C_4H_9)_4NBr$, powdered NaOH, ether and/or ether/CH_2Cl_2 or alkyl halogenide, potassium-t-butylate, DMSO; (b) carboxylic acid, trifluoroacetic acid anhydride, polyphosphoric acid, CH_2Cl_2; (c) ethanolic potassium hydroxide or H_2, Pd/C, THF, if R^{19} = benzyl.

Method 3

To prepare the alkane acids 9 and/or 11 that are homologous to the 3-Acylindole-2-carboxylic acids, for example indole-2-alkane acid esters 2 can be used as starting materials. These are first acylated in position 3 of the indole using Vilsmeier or Friedel-Crafts synthesis. The ester 8 obtained can be alkylated on indole nitrogen to the compounds 10. The N-alkylation can be carried out as described in Method 1. The carboxylic acids 9 and/or 11 according to the invention are obtained from 8 and/or 10 using ester cleavage. The ester cleavage can be carried out hydrolytically, e.g. using alcoholic potassium hydroxide, or also hydrogenolytically in the case of the benzyl ester, e.g. in THF with hydrogen in the presence of Pd/C. The latter method is mainly indicated if in addition to this ester group other functions sensitive to hydrolysis are contained in the compounds.

Method 3

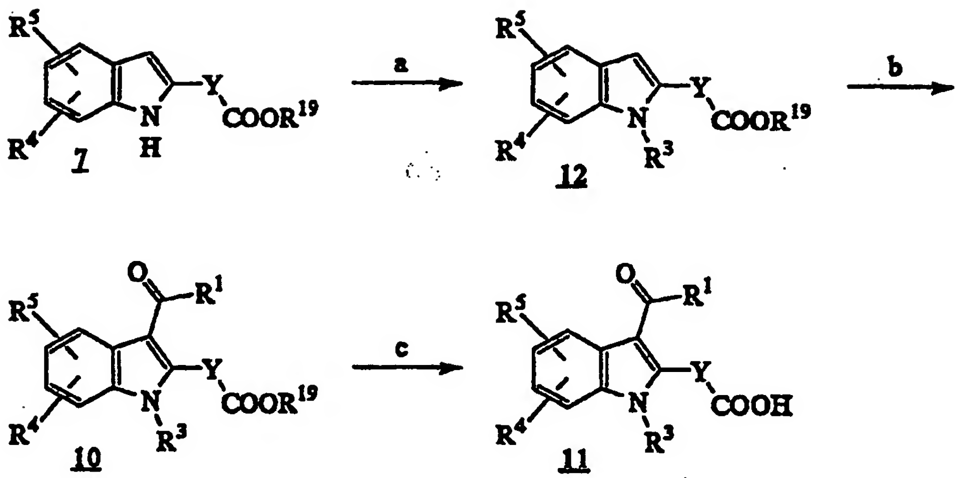


a) Carboxylic acid dimethylamide, $POCl_3$, benzene; (b) ethanolic potassium hydroxide or H_2, Pd/C, THF, if R^{19} = benzyl; (c) p-toluenesulfonic acid ester and/or alkyl halogenide, $(C_4H_9)_4NBr$, powdered NaOH, ether and/or ether/CH_2Cl_2 or alkyl halogenide, potassium-t-butylate, DMSO.

Method 4

Compounds of formula 11 can also be prepared alternatively according to Method 4. The reactions correspond in principle to the reactions in Method 3. However, in this case, the indole-2-carboxylic acid ester 7 is first N-alkylated and, only after that, acylated in position 3 of the indole.

Method 4

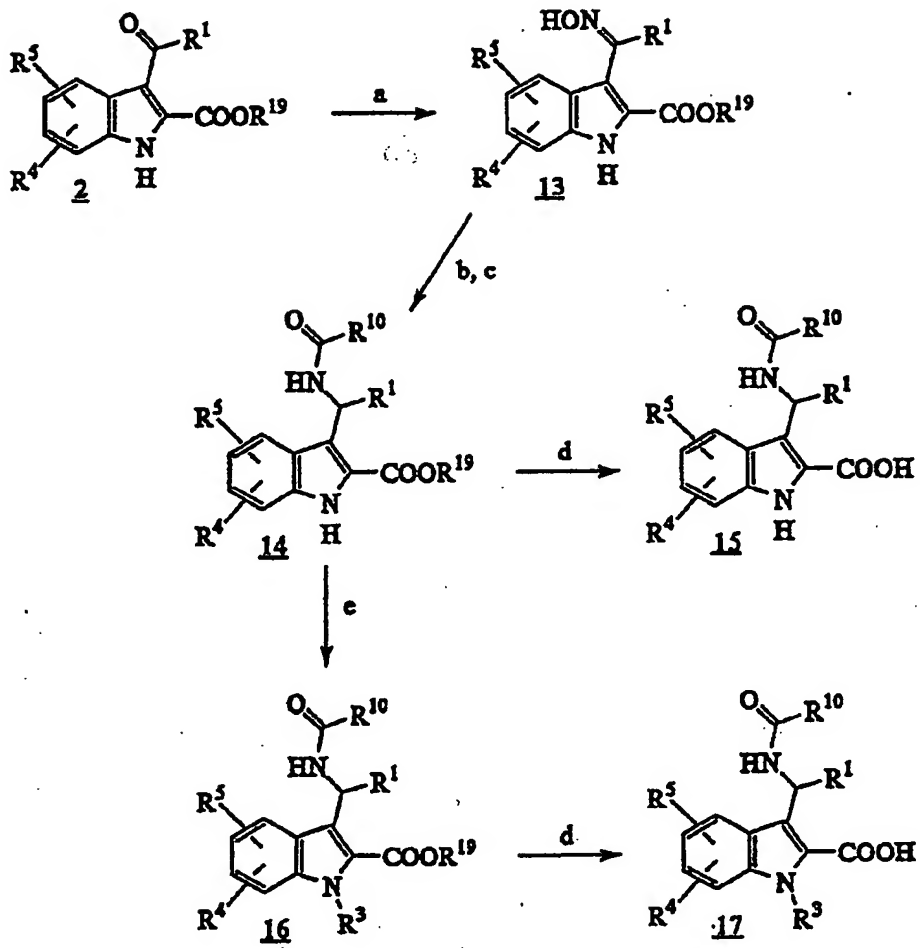


a) p-Toluenesulfonic acid ester and/or alkyl halogenide, $(C_4H_9)_4NBr$, powdered NaOH, ether and/or ether/CH_2Cl_2 <u>or</u> alkyl halogenide, potassium-t-butylate, DMSO; (b) carboxylic acid dimethylamide, $POCl_3$, benzene; c) ethanolic potassium hydroxide <u>or</u> H_2, Pd/C, THF, if R^{19} = benzyl.

<u>Method 5</u>

3-(1-Acylaminoalkyl)indole-2-alkane acids <u>15</u> and/or <u>17</u> can be prepared with the reaction sequence indicated in Method 5. Starting materials in this process are 3-Acylindole-2-carboxylic acid ester <u>2</u> (see Method 1). These are first reductively animated at the keto group; the amination is carried out e.g. by reaction with hydroxylamine-hydrochloride, e.g. in ethanol/pyridine or with ethanol/$BaCO_3$, to the oximes <u>13</u> and subsequent reduction of the oximes with zinc in sodium acetate/glacial acetic acid. Acylation of the amine function obtained, e.g. with carboxylic acid chlorides in the presence of dimethylaminopyridine in triethylamine/chloroform, leads to the compounds <u>14</u>. These can be alkylated on indole nitrogen to the compounds <u>16</u>. The N-alkylation can be carried out as described in Method 1. The carboxylic acids <u>15</u> and/or <u>17</u> according to the invention are obtained from <u>14</u> and/or <u>16</u> by ester cleavage. The ester cleavage can be carried out hydrolytically, e.g. with alcoholic potassium hydroxide, or also hydrogenolytically in the case of benzyl ester, e.g. in THF with hydrogen in the presence of Pd/C. The latter method is mainly indicated if, in addition to this ester group, other functions sensitive to hydrolysis are contained in the compounds.

Method 5

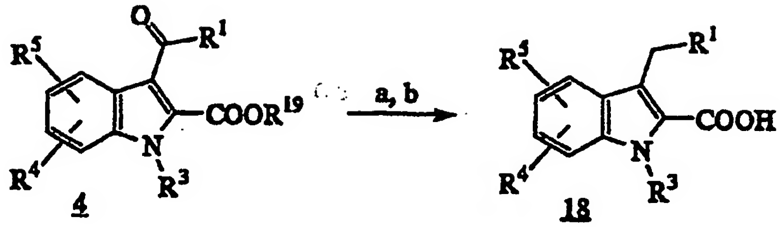


a) Hydroxylamine-hydrochloride, ethanol, pyridine; (b) zinc, sodium acetate, glacial acetic acid; (c) acyl chloride, 4-dimethylaminopyridine, triethylamine, $CHCl_3$; (d) ethanolic potassium hydroxide or H_2, Pd/C, THF, if R^{19} = benzyl; (e) p-toluenesulfonic acid ester and/or alkyl halogenide, $(C_4H_9)_4NBr$, powdered NaOH, ether and/or ether/CH_2Cl_2 or alkyl halogenide, potassium-t-butylate, DMSO.

Method 6

Compounds according to the invention in which Q stands for CH_2 can be prepared, for example, from the 3-acylindole derivatives 4 and/or 10. By reduction of the keto group, e.g. using $NaBH_4/BF_3$-ethyl ether complex in a suitable solvent and/or solvent mixture, like THF/methyl acetate and then subsequent ester cleavage, the desired indole derivatives 18 are obtained. The preparation of these compounds from 4 and/or 10 is also possible alternatively, e.g. using the Wolff-Kishner reduction.

Method 6



a) $NaBH_4$, BF_3-Ethyl ester complex, THF, Methyl acetate; (b) ethanolic potassium hydroxide <u>or</u> H_2, Pd/C, THF, if R^{19} = benzyl.

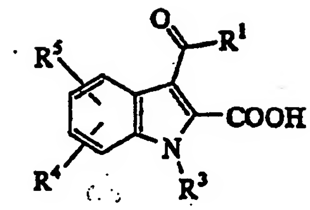
<u>Method 7</u>

Compounds according to the invention, in which R^2 stands for –Tz, or –Y-Tz, whereby Y can be a C_1-C_8-alkyl and/or C_2-C_8-alkenyl group, that may be interrupted by an oxygen heteroatom and Tz indicates 1H or 2H tetrazol-5-yl, can be prepared as known, for example, from analogous compounds in which R^2 stands for –COOH or –Y-COOH (see e.g. US Patent 4,808,608).

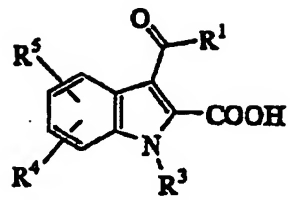
Representative Compounds

Tables 1 to 4 show representative compounds of the invention.

Table 1

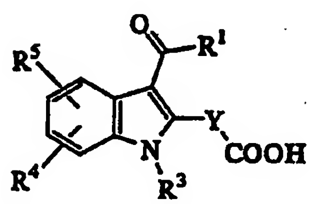


Example No.	R^1	R^3	R^4/R^5
1	$C_{17}H_{35}$	H	H/H
2	$C_{17}H_{35}$	CH_3	H/H
3	C_7H_{15}	CH_3	H/H
4	C_9H_{19}	CH_3	H/H
5	$C_{11}H_{23}$	CH_3	H/H
6	$C_{13}H_{27}$	CH_3	H/H
7	$(CH_2)_8CH=CH_2$	CH_3	H/H
8	4-Hexylphenyl	CH_3	H/H
9	2-Dodecyloxyphenyl	CH_3	H/H
10	3-Dodecyloxyphenyl	CH_3	H/H
11	4-Dodecyloxyphenyl	CH_3	H/H
12	$C_{17}H_{35}$	C_6H_{13}	H/H
13	$C_{17}H_{35}$	$C_{12}H_{25}$	H/H
14	$C_{17}H_{35}$	$C_{18}H_{37}$	H/H
15	$C_{17}H_{35}$	3-phenylpropyl	H/H
16	$C_{17}H_{35}$	Benzyl	H/H
17	$C_{17}H_{35}$	4-Chlorobenzyl	H/H
18	$C_{17}H_{35}$	4-Methylbenzyl	H/H
19	$C_{17}H_{35}$	4-Carbamoylbenzyl	H/H
20	$C_{17}H_{35}$	4-Methoxybenzyl	H/H



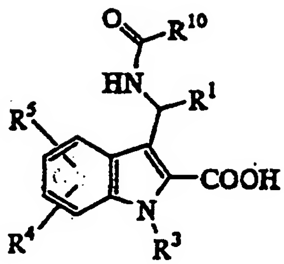
Example No.	R^1	R^3	R^4/R^5
21	$C_{17}H_{35}$	3-Pyridylmethyl	H/H
22	$C_{17}H_{35}$	4-Cyanobenzyl	H/H
23	$C_{17}H_{35}$	4-Hydroxybenzyl	H/H
24	$C_{17}H_{35}$	3-Hydroxypropyl	H/H
25	$C_{17}H_{35}$	CH_3	4-Cl/H
26	$C_{17}H_{35}$	CH_3	5-Cl/H
27	$C_{17}H_{35}$	CH_3	5-OCH_3/H

Table 2



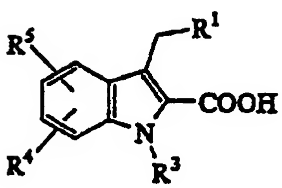
Example No.	R^1	R^3	R^4/R^5	Y
28	$C_{17}H_{35}$	H	H/H	CH_2
29	$C_{17}H_{35}$	CH_3	H/H	CH_2
30	$C_{17}H_{35}$	H	H/H	CH_2CH_2
31	$C_{17}H_{35}$	CH_3	H/H	CH_2CH_2

Table 3



Example No.	R^1	R^3	R^4/R^5	R^{10}
32	$C_{17}H_{35}$	H	H/H	$C_{17}H_{35}$
33	$C_{17}H_{35}$	H	H/H	3-Phenylpropyl
34	$C_{17}H_{35}$	H	H/H	CH_3
35	$C_{17}H_{35}$	CH_3	H/H	$C_{17}H_{35}$
36	$C_{17}H_{35}$	CH_3	H/H	3-Phenylpropyl
37	$C_{17}H_{35}$	CH_3	H/H	CH_3

Table 4



Example No.	R^1	R^3	R^4/R^5
38	$C_{17}H_{35}$	CH_3	H/H

The following examples explain the invention.

The batches were prepared with exclusion of oxygen from the air. Silica gel 60 (70-230 mesh ASTM) from the Merck Company, Darmstadt, was used for column chromatography (SC); for application on the columns the substances were dissolved in solvents with elution strength that was lower than the elution strength of the respectively specified eluent (usually toluene, $CHCl_3$ or CH_2Cl_2 and/or mixtures of these solvents with petrol ether). All temperature data are uncorrected. During recording of the mass spectra, ionization was carried out chemically using CH_4 gas and/or CH_5^+ ions. The NMR spectra are 400 MHz spectra that were measured in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard.

Example 1

3-Octadecanoylindole-2-carboxylic acid

A. 3-Octadecanoylindole-carboxylic acid ethyl ester

The mixture of 2.27 g (12 mmol) indole-2-caroxylic acid ethyl ester, 5.12 g (18 mmol) octadecanoic acid, 550 mg polyphosphoric acid, 40 ml absolute CH_2Cl_2 and 2.6 ml trifluoroacetic acid anhydride is stirred 5 h at room temperature. Then it is mixed with saturated NaCl solution and extracted with ether. The organic phase is washed with 1 M NaOH containing NaCl and, after addition of diatomaceous earth for removal of the precipitated octadecanoate, it is suctioned off. The ether phase is dried using Na_2SO_4 and the solvent distilled off. The residue is chromatographed on silica gel, first with CH_2Cl_2/petrol ether 3:1 and then with CH_2Cl_2. After concentration of the eluate, the product remains as a solid material.
Yield: 2.28 g (42%)
Melting point: 65-68°C
$C_{29}H_{45}NO_3$ (455.7)
MS: m/z (rel. int.) = 456 (71%), 428 (100%)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.13-1.41 (m, 28H, $-(CH_2)_{14}-$), 1.43 (t, 3H, $-O-CH_2-\underline{CH_3}$, J = 7 Hz), 1.74 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.07 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 4.45 (q, 2H, $-O-\underline{CH_2}-CH_3$, J = 7 Hz), 7.24 (t, 1H, arom., J = 8 Hz), 7.37 (t, 1H, arom., J = 8 Hz), 7.42 (d, 1H, arom., J = 8 Hz), 7.91 (d, 1H, arom., J = 8 Hz), 9.05 (s, 1H, > NH)

B. 3-Octadecanoylindole-2-carboxylic acid

The mixture of 456 mg (1 mmol) 3-Octadecanoylindole-2-carboxylic acid ethyl ester, 15 ml ethanol and 5 ml 10% aqueous KOH solution is heated to boiling 1 h at reflux. Then it is mixed with water, acidified with 10% hydrochloric acid and extracted twice with CH_2Cl_2. The organic phases are washed with diluted hydrochloric acid, dried over Na_2SO_4 and concentrated. The product is precipitated from methanol.
Yield: 200 mg (47%)
Melting point: 148-150°C
$C_{27}H_{41}NO_3$ (427.6)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.12-1.48 (m, 28H, $-(CH_2)_{14}-$), 1.88 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.28 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 7.42-7.52 (m, 2H, arom.), 7.62 (d, 1H, arom., J = 8 Hz), 8.00 (d, 1H, arom., J = 8 Hz), 10.25 (s, 1H, > NH), 17.93 (s, 1H, -COOH)

Example 2

1-Methyl-3-octadecanoylindole-2-carboxylic acid

A. 1-Methyl-3-octadecanoylindole-2-carboxylic acid ethyl ester

The mixture of 456 mg (1 mmol) 3-Octadecanoylindole-2-carboxylic acid ethyl ester (see Example 1 A), 205 mg (1.1 mmol) p-toluenesulfonic acid methyl ester, 32 mg (0.1 mmol) tetrabutylammonium bromide, 10 ml ether and 48 mg (1.2 mmol) powdered NaOH is stirred 6 h at room temperature. Then it is mixed with water and extracted twice with ether, whereby NaCl is added for better phase separation. The extracts are dried over Na_2SO_4 and the solvent is distilled off. The residue is chromatographed with petrol ether/ethyl acetate 9:1. After concentration of the eluates, the product remains as a solid material.
Yield: 350 mg (75%)
Melting point: 45-48°C
$C_{30}H_{47}NO_3$ (469.7)
MS: m/z (rel. int.) = 470 (61%), 442 (100%)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.07-1.39 (m, 28H, $-(CH_2)_{14}-$), 1.42 (t, 3H, $-O-CH_2-\underline{CH_3}$, J = 7 Hz), 1.75 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 2.90 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 3.90 (s, 3H, > $N-CH_3$), 4.47 (q, 2H, $-O-\underline{CH_2}-CH_3$, J = 7 Hz), 7.26-7.30 (m, 1H, arom.), 7.35-7.40 (m, 2H, arom.), 7.94 (d, 1H, arom., J = 8 Hz)

B. 1-Methyl-3-octadecanoylindole-2-carboxylic acid

164 mg (0.35 mmol) 1-Methyl-3-octadecanoylindole-2-carboxylic acid ethyl ester is saponified according to Example 1 B. The product is precipitated from methanol.
Yield: 123 mg (80%)
Melting point: 108-111°C
$C_{28}H_{43}NO_3$ (441.7)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.14-1.43 (m, 26H, $-(CH_2)_{13}-$), 1.48 (quint, 2H, $-\underline{CH_2}-$, J = 7 Hz), 1.86 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.28 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 4.27 (s, 3H, > $N-CH_3$), 7.45 (t, 1H, arom., J = 8 Hz), 7.51 (t, 1H, arom., J = 8 Hz), 7.61 (d, 1H, arom., J = 8 Hz), 8.02 (d, 1H, arom., J = 8 Hz), 16.70 (s, 1H, -COOH)

Example 3

1-Methyl-3-octanoylindole-2-carboxylic acid

A. 1-Methylindole-2-carboxylic acid ethyl ester

The mixture of 1.89 g (10 mmol) indole-2-carboxylic acid ethyl ester, 2.05 g (11 mmol) p-toluenesulfonic acid methyl ester, 0.32 g (1 mmol) tetrabutylammonium bromide, 100 ml ether and 0.48 g (12 mmol) powdered NaOH is stirred 12 h at room temperature. Then the mixture is suctioned off and then filter cake washed twice with ether. The combined ether phases are concentrated and the residue is chromatographed on silica gel with petrol ether/ethyl acetate 19:1. The oil remaining after concentration of the eluate crystallizes after some time (see Johnson et al., J. Am. Chem. Soc. 1945, 67, 428)
Yield: 1.54 g (76%)
Melting point: 63-64°C
$C_{12}H_{13}NO_2$ (203.2)
^{1}H-NMR: δ (ppm) = 1.41 (t, 3H, -O-CH$_2$-<u>CH$_3$</u>, J = 7 Hz), 4.09 (s, 3H, > N-$_{CH3}$), 4.38 (q, 2H, -O-<u>CH$_2$</u>-CH$_3$, J = 7 Hz), 7.15 (t, 1H, arom., J = 8 Hz), 7.31 (s, 1H, arom.), 7.33-7.40 (m, 2H, arom.), 7.68 (d, 1H, arom., J = 8 Hz)

B. 1-Methyl-3-octanoylindole-2-carboxylic acid

The mixture of 122 mg (0.6 mmol) 1-Methylindole-2-carboxylic acid ethyl ester, 130 mg (0.9 mmol) octanoic acid, 27 mg polyphosphoric acid, 3 ml absolute CH_2Cl_2 and 0.13 ml trifluoroacetic acid anhydride is stirred 4 h at room temperature. Then it is mixed with saturated NaCl solution and extracted with ether. The organic phase is washed with 1 M NaOH containing NaCl and dried over Na_2SO_4. The solvent is distilled off, the residue is chromatographed on silica gel with petrol ether/ethyl acetate 9:1 and the 1-methyl-3-octanoylindole-2-carboxylic acid ethyl ester is saponified according to Example 1 B, whereby ether is used to extract the carboxylic acid formed instead of CH_2Cl_2. The product is precipitated from petrol ether.
Yield: 71 mg (38%)
Melting point: 113-114°C
$C_{18}H_{23}NO_3$ (311.5)
^{1}H-NMR: δ (ppm) = 0.90 (t, 3H, -CH$_3$, J = 7 Hz), 1.23-1.52 (m, 6H, -(CH$_2$)$_3$-), 1.48 (quint, 2H, -CH$_2$-, J = 7 Hz), 1.86 (quint, 2H, -<u>CH$_2$</u>-CH$_2$-CO-, J = 7 Hz), 3.28 (t, 2H, CH$_2$-CO-, J = 7 Hz), 4.27 (s, 3H, > N-CH$_3$), 7.43-7.53 (m, 2H, Arom), 7.61 (d, 1H, arom., J = 8 Hz), 8.01 (d, 1H, arom., J = 8 Hz), 16.73 (s, 1H, -COOH)

Example 4

3-Decanoyl-1-methylindole-2-carboxylic acid

Preparation according to Example 3 B with 155 mg (0.9 mmol) decanoic acid instead of octanoic acid.
Yield: 46 mg (23)
Melting point: 114-116°C
$C_{20}H_{27}NO_3$ (329.4)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, -CH$_3$, J = 7 Hz), 1.23-1.41 (m, 10H, -(CH$_2$)$_5$-), 1.48 (quint, 2H, -CH$_2$-, J = 7 Hz), 1.86 (quint, 2H, -<u>CH$_2$</u>-CH$_2$-CO-, J = 7 Hz), 3.28 (t, 2H, -CH$_2$-CO-, J = 7 Hz), 4.27 (s, 3H, > N-CH$_3$), 7.43-7.53 (m, 2H, arom.), 7.61 (d, 1H, arom., J = 9 Hz), 8.02 (d, 1H, arom., J = 8 Hz), 16.71 (s, 1H, -COOH)

Example 5

3-Dodecanoyl-1-methylindole-2-carboxylic acid

Preparation according to Example 3 B with 182 mg (0.9 mmol) dodecanoic acid instead of octanoic acid. As a deviation, in the column chromatography, elution is carried out with petrol ether/ethyl acetate 19:1.
Yield: 49 mg (23%)
Melting point: 116-117°C
$C_{22}H_{31}NO_3$ (357.5)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, -CH$_3$, J = 7 Hz), 1.16-1.43 (m, 14H, -(CH$_2$)$_7$-), 1.48 (quint, 2H, -CH$_2$-, J = 7 Hz), 1.86 (quint, 2H, -<u>CH$_2$</u>-CH$_2$-CO-, J = 7 Hz), 3.28 (t, 2H, -CH$_2$-CO-, J = 7 Hz), 4.27 (s, 3H, > N-CH$_3$), 7.43-7.53 (m, 2H, arom.), 7.61 (d, 1H, arom., J = 8 Hz), 8.02 (d, 1H, arom., J = 9 Hz), 16.72 (s, 1H, -COOH)

Example 6

1-Methyl-3-tetradecanoylindole-2-carboxylic acid

Preparation according to Example 3 B with 206 mg (0.9 mmol) tetradecanoic acid instead of octanoic acid. As a deviation from that example, the isolation of the 1-methyl-3-tetradecanoylindole-2-carboxylic acid ethyl ester is carried out according to Example 1 B; in the column chromatography, elution is carried out using petrol ether/ethyl acetate 19:1.
Yield: 33 mg (14%)
Melting point: 118-119°C
$C_{24}H_{35}NO_3$ (385.5)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.16-1.43 (m, 18H, $-(CH_2)_9-$), 1.47 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.86 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.28 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 4.27 (s, 3H, > $N-CH_3-$), 7.43-7.53 (m, 2H, arom.), 7.61 (d, 1H, Arom, J = 8 Hz), 8.02 (d, 1H, Arom, J = 9 Hz), 16.72 (s, 1H, -COOH)

Example 7

1-Methyl-3-(10-undecenol)indole-2-carboxylic acid

Preparation according to Example 3 B with 166 mg (0.9 mmol) 10-undecenoic acid instead of octanoic acid. As a deviation from that example, in the column chromatography, elution is carried using petrol ether/ethyl acetate 19:1.
Yield: 54 mg (26%)
Melting point: 93 – 95°C
$C_{21}H_{27}NO_3$ (341.5)
^{1}H-NMR: δ (ppm) = 1.23-1.43 (m, 8H, $-(CH_2)_4-$), 1.48 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.86 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 2.05 (q, 2H, $-\underline{CH_2}-CH-CH_2-$, J = 7 Hz), 3.28 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 4.27 (s, 3H, > $N-CH_3-$), 4.92-5.02 (m, 2H, $-CH-\underline{CH_2}-$), 5.76-5.86 (m, 1H, $-\underline{CH}-CH_2-$) 7.43-7.53 (m, 2H, arom.), 7.61 (d, 1H, Arom, J = 9 Hz), 8.01 (d, 1H, Arom, J = 9 Hz), 16.72 (s, 1H, -COOH)

Example 8

3-(4-Hexylbenzoyl)-1-methylindole-2-carboxylic acid

Preparation according to Example 3 B with 206 mg (0.9 mmol) 4-hexylbenzoic acid instead of octanoic acid. As a deviation from that example, in the column chromatography, elution is carried using petrol ether/ethyl acetate 19:1.
Yield: 32 mg (15%)
Melting point: 114 – 116°C
$C_{23}H_{25}NO_3$ (363.5)
^{1}H-NMR: δ (ppm) = 0.90 (t, 3H, $-CH_3$, J = 7 Hz), 1.24-1.46 (m, 6H, $-(CH_2)_3-$), 1.46-1.66 (m, 2H, $-CH_2-$), 1.68 (quint, 2H, Phenyl-$CH_2-\underline{CH_2}-$, J = 7 Hz), 2.73 (t, 2H, -Phenyl-CH_2-, J = 7 Hz), 4.26 (s, 3H, > $N-CH_3$), 6.98 (d, 1H, arom., J = 8 Hz), 7.11 (t, 1H, arom., J = 8 Hz), 7.31 (d, 2H, arom., J = 8 Hz), 7.41 (t, 1H, Arom, J = 8 Hz), 7.54 (d, 1H, Arom, J = 8 Hz), 7.73 (d, 2H, Arom, J = 8 Hz), 14.58 (broad, 1H, -COOH)

Example 9

3-(2-Dodecylbenzoyl)-1-methylindole-2-carboxylic acid

Preparation according to Example 3 B with 276 mg (0.9 mmol) 3-dodecyloxybenzoic acid instead of octanoic acid. As a deviation from that example, in the column chromatography, elution is carried using petrol ether/ethyl acetate 19:1.
Yield: 79 mg (28%)
Melting point: 63-65°C
$C_{29}H_{37}NO_4$ (463.6)
^{1}H-NMR: δ (ppm) = 0.72 (quint, 2H, $-CH_2-$, J = 7 Hz), 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 0.92-1.04 (m, 4H, $-CH_2-$ and $-CH_2-$), 1.04-1.15 (m, 2H, $-CH_2-$), 1.15-1.32 (m, 12H, $-(CH_2)_6-$), 3.75 (t, 2H, $-O-CH_2-$, J = 6 Hz), 4.28 (s, 3H, > $N-CH_3$), 6.65 (d, 1H, arom., J = 7 Hz), 6.98 (d, 1H, arom., J = 8 Hz), 7.05 (t, 1H, arom., J = 8 Hz), 7.12 (t, 1H, arom., J = 7 Hz), 7.36 (t, 1H, arom., J = 7 Hz), 7.47 (t, 1H, arom., J = 7 Hz), 7.50 (t, 1H, arom., J = 8 Hz), 7.57 (t, 1H, arom., J = 8 Hz), 16.06 (s, 1H, -COOH)

Example 10

3-(3-Dodecylbenzoyl)-1-methylindole-2-carboxylic acid

Preparation according to Example 3 B with 276 mg (0.9 mmol) 3-dodecyloxybenzoic acid instead of octanoic acid. As a deviation from that example, in the column chromatography, elution is carried using petrol ether/ethyl acetate 19:1.
Yield: 18 mg (6%)
Melting point: 118 – 120°C
$C_{29}H_{37}NO_4$ (463.6)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, -CH_3, J = 7 Hz), 1.18-1.37 (m, 16H, -$(CH_2)_8$-), 1.43 (quint, 2H, -CH_2-, J = 7 Hz), 1.77 (quint, 2H, -O-CH_2-$\underline{CH_2}$-, J = 7 Hz), 3.97 (t, 2H, -O-CH_2-, J = 7 Hz), 4.27 (s, 3H, > N-CH_3), 6.96 (d, 1H, arom., J = 8 Hz), 7.11 (t, 1H, arom., J = 8 Hz), 7.19-7.22 (m, 1H, arom.), 7.30-7.32 (m, 2H, arom.), 7.37-7.42 (m, 2H, arom.), 7.54 (d, 1H, arom., J = 8 Hz), 14.92 (broad, 1H, -COOH)

Example 11

3-(4-Dodecylbenzoyl)-1-methylindole-2-carboxylic acid

Preparation according to Example 3 B with 276 mg (0.9 mmol) 4-dodecyloxybenzoic acid instead of octanoic acid. As a deviation from that example, in the column chromatography, elution is carried using petrol ether/ethyl acetate 19:1.
Yield: 95 mg (34%)
Melting point: 90 – 92°C
$C_{29}H_{37}NO_4$ (463.6)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, -CH_3, J = 7 Hz), 1.18-1.41 (m, 16H, -$(CH_2)_8$-), 1.49 (quint, 2H, -CH_2-, J = 7 Hz), 1.84 (quint, 2H, -O-CH_2-$\underline{CH_2}$-, J = 7 Hz), 4.07 (t, 2H, -O-CH_2-, J = 7 Hz), 4.25 (s, 3H, > N-CH_3-), 6.96 (d, 2H, arom., J = 9 Hz), 7.11-7.15 (m, 2H, arom.), 7.39-7.43 (m, 1H, arom.), 7.53 (d, 1H, arom., J = 9 Hz), 7.82 (d, 2H, arom., J = 9 Hz), 8 Hz), 14.75 (broad, 1H, -COOH)

Example 12

1-Hexyl-3-octadecanoylindole-2-carboxylic acid

The mixture of 189 mg (1 mmol) Indole-2-carboxylic acid ethyl ester, 135 mg (1.2 mmol) potassium-t-butylate and 4 ml absolute DMSO is stirred 15 min in an oil bath at 110°C. Then 198 mg (1.2 mmol) 1-bromohexane is added and the mixture is heated 15 minutes longer. After cooling, it is mixed with water and extracted with ether. The organic phase is dried over Na_2SO_4 and the solvent is distilled off. To the residue are added 427 mg (1.5 mmol) octadecanoic acid, 67 mg polyphosphoric acid, 6 ml absolute CH_2Cl_2 and 0.33 ml trifluoroacetic acid anhydride. The mixture is stirred 4 h at room temperature, then mixed with saturated NaCl solution and extracted with ether. The organic phase is washed with 1 M NaOH containing NaCl and suctioned off after the addition of diatomaceous earth to remove the precipitated octadecanoate. The ether phase is dried over Na_2SO_4 and the solvent is distilled off. The residue is chromatographed on silica gel with petrol ether ethyl acetate 29:1 and the 1-Alkyl-3-octadecanoylindole-2-carboxylic acid ethyl ester obtained is saponified according to Example 1 B, whereby the ether is used instead of CH_2Cl_2 for extraction of the carboxylic acid formed.
Yield: 66 mg (13%)
Melting point: 75 – 77°C
$C_{33}H_{53}NO_3$ (511.8)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, -CH_3, J = 7 Hz), 0.89 (t, 3H, -CH_3, J = 7 Hz), 1.16-1.55 (m, 34H, -$(CH_2)_3$- and -$(CH_2)_{14}$-), 1.86 (quint, 4H, -$\underline{CH_2}$-CH_2-CO- and -$\underline{CH_2}$-CH_2-N <, J = 7 Hz), 3.27 (t, 2H, -CH_2-CO-, J = 7 Hz), 4.79 (t, 2H, -CH_2-N <, J = 7 Hz), 7.44 (t, 1H, arom., J = 8 Hz), 7.49 (t, 1H, arom., J = 8 Hz), 7.59 (d, 1H, arom., J = 8 Hz), 8.01 (d, 1H, arom., J = 8 Hz), 16.67 (broad, 1H, -COOH)

Example 13

1-Dodecyl-3-octadecanoylindole-2-carboxylic acid

Preparation according to Example 12 with 299 mg (1.2 mmol) 1-Bromododecane instead of 1-Bromohexane. As a deviation from that example, in the column chromatography, elution is carried using petrol ether/ethyl acetate 200:3.
Yield: 135 mg (23%)
Melting point: 75 – 77°C
$C_{39}H_{65}NO_3$ (596.0)
^{1}H-NMR: δ (ppm) = 0.88 (t, 6H, -CH_3 and -CH_3, J = 7 Hz), 1.11-1.52 (m, 46H, -$(CH_2)_9$- and -$(CH_2)_{14}$-), 1.86 (quint, 4H, -$\underline{CH_2}$-CH_2-CO- and -$\underline{CH_2}$-CH_2-N <, J = 7 Hz), 3.27 (t, 2H, -CH_2-CO-, J = 7 Hz), 4.79 (t, 2H, -CH_2-N <, J = 7 Hz), 7.44 (t, 1H, arom., J = 8 Hz), 7.49 (t, 1H, arom., J = 8 Hz), 7.59 (d, 1H, arom., J = 8 Hz), 8.01 (d, 1H, arom., J = 8 Hz), 16.73 (broad, 1H, -COOH)

Example 14

1-Octadecyl-3-octadecanoylindole-2-carboxylic acid

Preparation according to Example 12 with 398 mg (1.2 mmol) 1-Bromooctadecane instead of 1-Bromohexane. As a deviation from that example, in the column chromatography, elution is carried using petrol ether/ethyl acetate 200:3.
Yield: 174 mg (26%)
Melting point: 83 – 84°C
$C_{45}H_{77}NO_3$ (680.1)
^{1}H-NMR: δ (ppm) = 0.88 (t, 6H, -CH_3 and -CH_3, J = 7 Hz), 1.14-1.52 (m, 58H, -$(CH_2)_{15}$- and -$(CH_2)_{14}$-), 1.86 (quint, 4H, -$\underline{CH_2}$-CH_2-CO- and -$\underline{CH_2}$-CH_2-N < , J = 7 Hz), 3.27 (t, 2H, -CH_2-CO-, J = 7 Hz), 4.79 (t, 2H, -CH_2-N <, J = 7 Hz), 7.44 (t, 1H, arom., J = 8 Hz), 7.49 (t, 1H, arom., J = 8 Hz), 7.59 (d, 1H, arom., J = 8 Hz), 8.01 (d, 1H, arom., J = 8 Hz), 16.71 (broad, 1H, -COOH)

Example 15

1-Octadecanoyl-1-(3-phenylpropyl)indole-2-carboxylic acid

Preparation according to Example 12 with 239 mg (1.2 mmol) 1-Bromo-3-phenylpropane instead of 1-Bromohexane.
Yield: 156 mg (29%)
Melting point: 73 – 74°C
$C_{36}H_{31}NO_3$ (545.8)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, -CH_3, J = 7 Hz), 1.14-1.41 (m, 26H, -$(CH_2)_{13}$-), 1.47 (quint, 2H, -CH_2-, J = 7 Hz), 1.85 (quint, 4H, -$\underline{CH_2}$-CH_2-CO-, J = 7 Hz), 2.22 (quint, 2H, -CH_2-CH_2-N <, J = 7 Hz), 2.79 (t, 2H, Phenyl-CH_2, J = 7 Hz), 3.26 (t, 2H, -CH_2-CO-, J = Hz), 4.81 (t, 2H, -CH_2-N <, J = 7 Hz) 7.20-7.43 (m, 8H, arom.), 7.98-8.00 (m, 1H, arom.), 16.72 (broad, 1H, -COOH)

Example 16

1-Benzyl-3-octadecanoylindole-2-carboxylic acid

Preparation according to Example 12 with 205 mg (1.2 mmol) Benzyl bromide instead of 1-Bromohexane. As a deviation from that example, in the column chromatography, elution is carried using petrol ether/ethyl acetate 19:1.
Yield: 50 mg (10%)
Melting point: starting from 87°C
$C_{34}H_{47}NO_3$ (517.8)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, -CH_3, J = 7 Hz), 1.16-1.43 (m, 26H, -$(CH_2)_{13}$-), 1.49 (quint, 2H, -CH_2-, J = 7 Hz), 1.88 (quint, 4H, -$\underline{CH_2}$-CH_2-CO-, J = 7 Hz), 3.31 (t, 2H, -CH_2-CO-, J = 7 Hz), 6.13 (s, 2H, -CH_3-N <), 7.09 (d, 2H, arom., J = 7 Hz), 7.21-7.30 (m, 3H, arom.), 7.42-7.46 (m, 2H, arom.), 7.52-7.57 (m, 1H, arom.), 8.03-8.06 (m, 1H, arom.), 16.57 (broad, 1H, -COOH)

Example 17

1-(4-Chlorobenzyl)-3-octadecanoylindole-2-carboxylic acid

Preparation according to Example 12 with 193 mg (1.2 mmol) 4-Chlorobenzyl chloride instead of 1-Bromohexane. As a deviation from that example, in the column chromatography, elution is carried using petrol ether/ethyl acetate 19:1.
Yield: 18 mg (3%)
Melting point: 101 – 102°C
$C_{34}H_{46}ClNO_3$ (552.2)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, -CH_3, J = 7 Hz), 1.21-1.44 (m, 26H, -$(CH_2)_{13}$-), 1.48 (quint, 2H, -CH_2-, J = 7 Hz), 1.88 (quint, 4H, -$\underline{CH_2}$-CH_2-CO-, J = 7 Hz), 3.31 (t, 2H, -CH_2-CO-, J = 7 Hz), 6.07 (s, 2H, -CH_2-N <), 7.04 (d, 2H, arom., J = 9 Hz), 7.24 (d, 2H, arom., J = 9 Hz), 7.43-7.48 (m, 2H, arom.), 7.50-7.53 (m, 1H, arom.), 8.04-8.06 (m, 1H, arom.)

Example 18

1-(4-Methylbenzyl)-3-octadecanoylindole-2-carboxylic acid

Preparation according to Example 12 with 169 mg (1.2 mmol) 4-Methylbenzyl chloride instead of 1-Bromohexane. As a deviation from that example, in the column chromatography, elution is carried using petrol ether/ethyl acetate 19:1.
Yield: 109 mg (20%)
Melting point: 102 – 103°C
$C_{35}H_{49}NO_3$ (531.8)

^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.16-1.43 (m, 26H, $-(CH_{13}-)$, 1.48 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.88 (quint, 4H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 2.28 (s, 3H, Phenyl-CH_3), 3.30 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 6.09 (s, 2H, $-CH_2-N$ <), 7.00 (d, 2H, arom., J = 8 Hz), 7.06 (d, 2H, arom., J = 8 Hz), 7.41-7.45 (m, 2H, arom.), 7.55-7.60 (m, 1H, arom.), 8.01-8.05 (m, 1H, arom.), 16.54 (broad, 1H, -COOH)

Example 19

1-(4-Carbamoylbenzyl)-3-octadecanoylindole-2-carboxylic acid

Preparation according to Example 12 with 169 mg (1.2 mmol) 4-Cyanobenzyl bromide instead of 1-Bromohexane. As a deviation from that example, in the column chromatography, elution is carried using petrol ether/ethyl acetate 9:1. Also, after saponification, ether/CH_2Cl_2 3:1is used for extraction instead of ether; the product is precipitated from ether.
Yield: 39 mg (7%)
Melting point: 158 – 160°C
$C_{35}H_{48}N_2O_4$ (560.8) Calc. C 74.96 H 8.63 N 5.00
Found C 74.91 H 8.34 N 5.29
IR(KBr): Vmax = 3400 (N-H), 1690 (C=0), 1630 (C=0) cm^{-1}
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.14-1.45 (m, 26H, $-(CH_2)_{13}-$), 1.44 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.89 (quint, 4H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.33 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 5.56 (broad, 1H, > NH), 5.98 (broad, 1H, > NH), 6.15 (s, 2H, -CH_2-N <), 7.15 (d, 2H, arom., J = 8 Hz), 7.34-7.52 (m, 3H, arom.), 7.71 (d, 2H, arom., J = 8 Hz), 8.05-8.08 (m, 1H, arom.), 16.56 (broad, 1H, -COOH)

Example 20

1-(4-Methoxybenzyl)-3-octadecanoylindole-2-carboxylic acid

The mixture of 182 mg (0.4 mmol) 3-Octadecanoylindole-2-carboxylic acid ethyl ester (see Example 1 A), 49 mg (0.44 mmol) potassium-t-butylate and 3 ml absolute DMSO and 69 mg (0.44 mmol) 4-Methoxybenzyl chloride is stirred 15 min in an oil bath at 110°C. After cooling, it is mixed with water and extracted with ether. The organic phase is dried over Na_2SO_4 and the solvent is distilled off. The residue is chromatographed on silica gel with petrol ether/ethyl acetate 19:1 and the 1-(4-Methoxybenzyl)-3-octadecanoylindole-2-carboxylic acid obtained is saponified according to Example 1 B, whereby ether is used instead of CH_2Cl_2 for extraction of the carboxylic acid formed. The product is precipitated from petrol ether.
Yield: 57 mg (10%)
Melting point: 110 – 113°C
$C_{35}H_{49}NO_4$ (547.8)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.16-1.43 (m, 26H, $-(CH_2)_{13}-$), 1.48 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.87 (quint, 4H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.30 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 3.75 (s, 3H $-O-CH_3$), 6.06 (s, 2H, $-CH_2-N$ <), 6.79 (d, 2H, arom., J = 9 Hz), 7.08 (d, 2H, arom., J = 9 Hz), 7.41-7.46 (m, 2H, arom.), 7.59-7.62 (m, 1H, arom.), 8.01-8.04 (m, 1H, arom.), 16.59 (broad, 1H, -COOH)

Example 21

1-(3-Pyridylmethyl)-3-octadecanoylindole-2-carboxylic acid

The mixture of 182 mg (0.4 mmol) 3-Octadecanoylindole-2-carboxylic acid ethyl ester (see Example 1 A), 99 mg (0.88 mmol) potassium-t-butylate and 3 ml absolute DMSO and 69 mg (0.44 mmol) 4-Picolylchloride-Hydrochloride is stirred 15 min in an oil bath at 110°C. After cooling, it is mixed with saturated NaCl solution and extracted with ether. The organic phase is dried over Na_2SO_4 and the solvent is distilled off. The residue is chromatographed on silica gel with petrol ether/ethyl acetate 1.7:3 and 2.1:1. The 1-(3-Pyridylmethyl)-3-octadecanoylindole-2-carboxylic acid ethyl ester obtained is heated to boiling 1 h at reflux with 15 ml ethanol and 5 ml 10% aqueous KOH solution. After cooling, the mixture is diluted with phosphate buffer pH 4 and extracted twice with ether. The organic phases are washed with phosphate buffer pH 4, dried over Na_2SO_4 and concentrated. The product is precipitated from ethyl acetate.
Yield: 22 mg (4%)
Melting point: 132 – 133°C
$C_{33}H_{46}N_2O_3$ (518.7)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.20-1.43 (m, 26H, $-(CH_2)_{13}-$), 1.48 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.88 (quint, 4H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.31 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 6.12 (s, 2H, $-CH_2-N$ <), 7.18-7.22 (m, 1H, arom.), 7.43-7.49 (m, 3H, arom.), 7.52-7.59 (m, 1H, arom.), 8.05-8.07 (m, 1H, arom.), 8.48-8.51 (m, 2H, arom.)

Example 22

1-(4-Cyanobenzyl)-3-octadecanoylindole-2-carboxylic acid

A. 3-Octadecanoylindole-2-carboxylic acid benzyl ester

The mixture of 302 mg (1.2 mmol) Indole-2-carboxylic acid benzylester, 512 mg (1.8 mmol) octadecanoic acid, 55 mg polyphosphoric acid, 8 ml absolute CH_2Cl_2 and 0.26 trifluoroacetic acid anhydride is stirred 10 min at room temperature. Then it is mixed with saturated NaCl solution and extracted with ether. The organic phase is washed with 1 M NaOH containing NaCl and suctioned off after the addition of diatomaceous earth to remove the precipitated octadecanoate. The ether phase is dried over Na_2SO_4 and the solvent is distilled off. The residue is chromatographed on silica gel with petrol ether ethyl acetate 1.19:1 and 2.9:1. After concentration of the eluates the product remains as a solid material.
Yield: 218 mg (35%)
Melting point: 82 – 85°C
$C_{34}H_{47}NO_3$ (517.8)
MS: m/z (rel.Int.) = 518 (37%), 490 (62%), 234 (35%), 91 (100%)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.13-1.37 (m, 28H, $-(CH_2)_{14}-$), 1.64 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 2.99 (t, 2H, $-\underline{CH_2}-CO-$, J = 7 Hz), 5.40 (s, 2H, $-COO-CH_2-$), 7.22-7.25 (m, 1H, arom.), 7.34-7.48 (m, 7H, arom.), 7.90 (d, 1H, arom., J = 9 Hz), 9.02 (s, 1H, > NH)

B. 1-(4-Cyanobenzyl)-3-octadecanoylindole-2-carboxylic acid

The mixture of 52 mg (0.1 mmol) 3-Octadecanoylindole-2-carboxylic acid benzylester, 22 mg (0.11 mmol) 4-Cyanobenzylbromide, 32 mg (0.1 mmol) Tetrabutylammonium bromide, 10 ml ether and 40 mg (1 mmol) powdered NaOH were heated 1 h, while being stirred to reflux. Then the mixture was suctioned off and the filter cake washed twice with ether/CH_2Cl_2 1:1. The filtrate was concentrated and the residue chromatographed on silica gel with petrol ether/ethyl acetate 1.9:1 and 2.17:3. The 1-(4-Cyanobenzyl)-3-octadecanoylindole-2-carboxylic acid obtained was dissolved in 5 ml THF and, after the addition of a spatula tip of Pd/C, hydrated 1.5 h at room temperature and normal pressure in hydrogen atmosphere with vigorous stirring. After the addition of diotomaceous earth, the mixture is filtered, the solvent distilled off and the product precipitated from petrol ether.
Yield: 15 mg (28%)
Melting point: 122-124°C
$C_{35}H_{46}N_2O_3$ (542.8)
IR (KBr): Vmax = 2240 (CN), 1705 (C=O) cm^{-1}
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.05-1.61 (m, 28H, $-(CH_2)_{14}-$), 1.89 (quint, 4H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.33 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 6.16 (s, 2H, $-CH_2-N<$), 7.16 (d, 2H, arom., J – 8 Hz), 7.46-7.49 (m, 3H, arom.), 7.57 (d, 2H, arom., J = 8 Hz), 8.07-8.09 (d, 1H, arom.), 16.58 (broad, 1H, -COOH)

Example 23

1-(4-Hydroxybenzyl)-3-octadecanoylindole-2-carboxylic acid

The solution of 27 mg (0.05 mmol) 1-(4-Methoxybenzyl)-3-octadecanoylindole-2-carboxylic acid (see Example 20) in 5 ml absolute CH_2Cl_2 is mixed at -20°C with the solution of 0.025 ml BBr_3 in 1 ml absolute CH_2Cl_2. The mixture is stirred 1 h at -20°C and then allowed to warm up for 1 h at room temperature. After addition of diluted hydrochloric acid, extraction is carried out twice with ether. The ether phases are dried over Na_2SO_4 and concentrated to a few ml. After addition of petrol ether and repeat concentration, the product precipitates.
Yield: 25 mg (94%)
Melting point: 119-122°C
$C_{34}4H_{47}NO_4$ (533.8)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.17-1.43 (m, 26H, $-(CH_2)_{13}-$), 1.48 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.87 (quint, 4H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.30 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 6.03 (s, 2H, $-CH_2-N <$), 6.70 (d, 2H, arom., J = 9 Hz), 7.01 (d, 2H, arom., J = 9 Hz), 7.42-7.48 (m, 2H, arom.), 7.60-7.62 (m, 1H, arom.), 8.02-8.04 (m, 1H, arom.), 16.70 (broad, 1H, -COOH)

Example 24

1-(3-Hydroxypropyl)-3-octadecanoylindole-2-carboxylic acid

A. 1-(3-Acetoxypropyl)-3-octadecanoylindole-2-carboxylic acid ethyl ester

The mixture of 114 mg (0.6 mmol) Indole-2-carboxylic acid ethyl ester, 67 mg (0.6 mmol) potassium-5-butylate and 3 ml absolute DMSO is stirred 15 min. in an oil bath at 110°C. Then the solution of 109 mg (0.6 mmol) acetic acid-(3-

bromopropyl)ester is added and the mixture is heated for 15 min. longer. After cooling, it is mixed with water and extracted with ether. The organic phase is dried over Na_2SO_4 and the solvent distilled off. To the residue, 228 mg (0.8 mmol) octadecanoic acid, 35 mg polyphosphoric acid, 3 ml absolute CH_2Cl_2 and 0.17 ml trifluoroacetic acid anhydride are added. The mixture is stirred 4 h at room temperature, then mixed with saturated NaCl solution and extracted with ether. The organic phase is washed with 1 M NaOH containing NaCl and suctioned off after addition of silica gel to remove the precipitated octadecanoate. The ether phase is dried over Na_2SO_4 and the solvent is distilled off. The residue is chromatographed on silica gel with petrol ether/ethyl acetate 9:1. The product remains as a waxy substance after removal of the eluent.
Yield: 97 mg (3%)
$C_{34}H_{53}NO_5$ (555.8)
MS: m/z (rel. int.) = 556 (56%), 528 (100%), 331 (40%)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.17-1.43 (m, 28H, $-(CH_2)_{14}-$), 1.41 (t, 3H, $-O-CH_2-\underline{CH_3}$, J = 7 Hz), 1.75 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 2.05 (s, 3H, $-CO-CH_3$), 2.17 (quint, 2H, $-\underline{CH_2}-CH_2-N<$, J = 6.4 Hz), 2.90 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 4.09 (t, 2H, $-CH_2-$, J = 6 Hz), 4.45 (q, 2H, $-O-\underline{CH_2}-CH_3$, J = 7 Hz), 4.45 (t, 2H, $-CH_2-$, J = 7 Hz), 7.27-7.30 (m, 1H, arom.), 7.35-7.41 (m, 2H, arom.), 7.90 (d, 1H, arom., J = 8 Hz)

B. 1-(3-Hydroxypropyl)-3-octadecanoylindole-2-carboxylic acid

The mixture of 83 mg (0.15 mmol) 1-(3-Acetoxypropyl)-3-octadecanoylindole-2-carboxylic acid ethyl ester, 15 ml ethanol and 5 ml 10% aqueous KOH solution is heated to boiling for 1.5 h at reflux. Then it is mixed with the solution of 4.1 g $Na_2HPO_4 \cdot H_2O$ in 80 ml water and extracted with ether. The organic phase is dried over Na_2SO_4 and concentrated. The product is precipitated from petrol ether.
Yield: 36 mg (49%)
Melting point: 77-80°C
$C_{30}H_{47}NO_4$ (485.7)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.16-1.42 (m, 26H, $-(CH_2)_{13}-$), 1.47 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.86 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$), J = 7 Hz), 2.15 (quint, 2H, $-\underline{CH_2}-CH_2-N<$, J = 6 Hz), 3.28 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 3.66 (t, 2H, $-CH_2-$, J = 6 Hz), 4.90-5.00 (m, 2H, $-CH_2$), 7.45 (t, 1H, J = 8 Hz), 7.50 (t, 1H, arom., J = 8 Hz), 7.69 (d, 1H, arom., J = 8 Hz), 8.01 (d, 1H, arom., J = 8 Hz)

Example 25

4-Chloro-1-methyl-3-octadecanoylindole-2-carboxylic acid

The mixture of 224 mg (1 mmol) 4-Chloroindole-2-carboxylic acid ethyl ester, 205 mg (1.1 mmol) p-toluenesulfonic acid methyl ester, 32 mg (0.1 mmol) tetrabutylammonium bromide, 10 ml ether and 48 mg (1.2 mmol) powdered NaOH is stirred at 8 h at room temperature. Then the mixture is suctioned off, the filter cake is washed with ether/CH_2Cl_2 1:1 and the solvent distilled off. To the residue, 427 mg (1.5 mmol) octadecanoic acid, 67 mg polyphosphoric acid, 6 ml absolute CH_2Cl_2 and 0.33 ml trifluoroacetic acid anhydride are added. The mixture is stirred 4 h at room temperature, then mixed with saturated NaCl solution and extracted with ether. The organic phase is washed with 1 M NaOH containing NaCl and suctioned off after the addition of diatomaceous earth to remove the precipitated octadecanoate. The ether phase is dried over Na_2SO_4 and concentrated. The residue is chromatographed on silica gel with petrol ether/ethyl acetate 19:1 and the 3-acylindole-2-carboxylic acid ester obtained is saponified according to Example 1 B, whereby ether is used to extract the carboxylic acid formed instead of CH_2Cl_2. The product is precipitated from petrol ether.
Yield: 130 mg (27%)
Melting point: 130-132°C
$C_{28}H_{42}ClNO_3$ (476.1)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.13-1.45 (m, 28H, $-(CH_2)_{14}-$), 1.80 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.02 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 4.08 (s, 3H, $> N-CH_3$), 7.18-7.34 (m, 3H, arom.)

Example 26

5-Chloro-1-methyl-3-octadecanoylindole-2-carboxylic acid

Preparation according to Example 25 with 5-chloroindole-2-carboxylic acid ethyl ester instead of 4-chloroindole-2-carboxylic acid ethyl ester.
Yield: 112 mg (24%)
Melting point: 97-99°C
$C_{28}H_{42}ClNO_3$ (476.1)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.16-1.42 (m, 26H, $-(CH_2)_{13}-$), 1.48 (quint, 2H, $-\underline{CH_2}-$, J = 7 Hz), 1.86 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.22 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 4.25 (s, 3H, $> N-CH_3$), 7.47 (dd, 1H, arom., J = 2 Hz and 9 Hz), 7.54 (d, 1H, arom., J = 9 Hz), 7.98 (d, 1H, arom., J = 2 Hz)

Example 27

5-Methoxy-1-methyl-3-octadecanoylindole-2-carboxylic acid

Preparation according to Example 25 with 219 mg (1 mmol) 5-methoxyindole-2-carboxylic acid ethyl ester instead of 4-chloroindole-2-carboxylic acid ethyl ester. However, the reaction time during the N-methylation is 15 h. The end product is precipitated from petrol ether and after that from methanol for further purification.
Yield: 42 mg (%) [no percentage indicated in original]
Melting point: 97-99°C
$C_{29}H_{45}NO_4$ (471.7)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.18-1.69 (m, 28H, $-(CH_2)_{14}-$), 1.86 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.21 (t, 2H, $-CH_2-CO-$, J = 7 Hz), 3.93 (s, 3H, $-CH_3$), 4.25 (s, 3H, $-CH_3$), 7.16 (dd, 1H, arom., J = 2 Hz and 9 Hz), 7.35 (s, 1H, arom.), 7.51 (d, 1H, arom., J = 9 Hz)

Example 28

3-Octadecanoylindol-2-yl-acetic acid

A. 3-Octadecanoylindol-2-yl-acetic acid ethyl ester

To a boiling solution of 374 mg (1.2 mmol) octadecanoic acid dimethylamide and 153 mg (1 mmol) $POCl_3$ in 10 ml absolute benzene, are added 203 mg (0.4 mmol) indol-2-yl-acetic acid ethyl ester (Capuano et al., Chem. Ber. 1986, 119, 2069-2074), dissolved in 3 ml absolute benzene and boiled 3 h at reflux. After the addition of a solution of 1 g sodium acetate in 4 ml water, the mixture is heated 15 min. longer with vigorous stirring at reflux. After cooling, the mixture is diluted with water and extracted twice with ether. The organic phases are dried over Na_2SO_4 and concentrated. The residue is chromatographed on silica gel with petrol ether/ethyl acetate 1.9:1 and 2.8:2 and the product precipitated from petrol ether.
Yield: 22 mg (47%)
Melting point: 86-97°C
$C_{30}H_{47}NO_3$ (469.7)
MS: m/z (rel. int.) = 470 (100%), 468 (16%), 424 (8%), 245 (9%)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.16-1.43 (m, 26H, $-(CH_2)_{13}-$), 1.32 (t, 3H, $-O-CH_2-\underline{CH_3}$, J = 7 Hz), 1.44 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.78 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.03 (t, 2H, $-CH_2-\underline{CH_2}-CO-$, J = 7 Hz), 4.26 (q, 2H, $-O-\underline{CH_2}-CH_3$, J = 7 Hz), 4.40 (s, 2H, $-CH_2-COO-$), 7.23-7.29 (m, 2H, arom.), 7.42-7.44 (m, 1H, arom.), 7.88-7.90 (m, 1H, arom.), 10.09 (s, 1H, > NH)

B. 3-Octadecanoylindol-2-yl-acetic acid

80 mg (0.17 mmol) 3-Octadecanoylindol-2-yl-acetic acid ethyl ester is saponified according to Example 1 B. However, the reaction time is only 15 min.; in addition, ether is used instead of CH_2Cl_2 to extract the carboxylic acid formed and the product is precipitated from petrol ether instead of from methanol.
Yield: 59 mg (79%)
Melting point: 134-136°C
$C_{28}H_{43}NO_3$ (441.7)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.16-1.41 (m, 26H, $-(CH_2)_{13}-$), 1.45 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.83 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.15 (t, 2H, $-CH_2-\underline{CH_2}-CO-$, J = 7 Hz), 4.12 (s, 2H, $-CH_2-COO-$), 7.28-7.35 (m, 2H, arom.), 7.45-7.47 (m, 1H, arom.), 7.81-7.83 (m, 1H, arom.), 10.17 (s, 1H, > NH)

Example 29

1-Methyl-3-octadecanoylindol-2-yl-acetic acid

The mixture of 80 mg (0.1 mmol) 3-Octadecanoylindol-2-yl-acetic acid ethyl ester (see Example 28 A), 32 mg (0.19 mmol) p-toluenesulfonic acid methyl ester, 22 mg (0.07 mmol) tetrabutylammonium bromide, 10 ml ether, 5 ml CH_2Cl_2 and 105 mg (2.6 mmol) powdered NaOH is stirred 20 h at room temperature. Then the mixture is suctioned off and the filter cake washed twice with ether/CH_2Cl_2 1:1. The filtrate is concentrated and the residue chromatographed on silica gel with petrol ether/ethyl acetate 17:3. The 1-Methyl-3-octadecanoylindol-2-yl-acetic acid ethyl ester is then saponified according to Example 28 B.
Yield: 22 mg (28%)
Melting point: 119-121°C
$C_{29}H_{45}NO_3$ (455.7)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.09-1.39 (m, 26H, $-(CH_2)_{13}-$), 1.45 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.83 (quint, 2H, $-\underline{CH_2}-CH_2-CO-$, J = 7 Hz), 3.15 (t, 2H, $-CH_2-\underline{CH_2}-CO-$, J = 7 Hz), 3.91 (s, 3H, > $N-CH_3$), 4.09 (s, 2H, $-CH_2-COO-$), 7.33-7.44 (m, 3H, arom.), 7.82-7.85 (m, 1H, arom.), 13.05 (s, 1H, -COOH)

Example 30

3-Octadecanoylindol-2-yl-propionic acid

A. 3-Octadecanoylindol-2-yl-propionic acid methyl ester

To a boiling solution of 137 mg (0.44 mmol) Octadecanoic acid dimethylamide and 61 mg (0.4 mmol) $POCl_3$ in 8 ml absolute benzene, is added 81 mg (0.4 mmol) indol-2-yl-propionic acid methyl ester (Capuano et al., Chem. Ber. 1986, 119, 2069-2074), dissolved in 2 ml absolute benzene and boiled 3 h at reflux. After addition of the solution of 1 g sodium acetate in 4 ml water, the mixture is heated 15 min. longer with vigorous stirring at reflux. After cooling, the mixture is diluted with water and extracted twice with ether. The organic phases are dried over Na_2SO_4 and concentrated. The product is precipitated from petrol ether.
Yield: 126 mg (67%)
Melting point: 91-93°C
$C_{30}H_{47}NO_3$ (469.7)
MS: m/z (rel. int.) = 470 (80%), 438 (100%)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.16-1.37 (m, 26H, $-(CH_2)_{13}-$), 1.43 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.78 (quint, 2H, -$\underline{CH_2}$-CH_2-CO-aryl, J = 7 Hz), 2.83 (t, 2H, $-CH_2-$, J = 6 Hz), 3.02 (t, 2H, $-CH_2$-CO-, J = 7 Hz), 3.46 (t, 2H, $-CH_2-$, J = 6 Hz), 3.67 (s, 3H, -O-CH_3), 7.21-7.25 (m, 2H, arom.), 7.37-7.40 (m, 1H, arom.), 7.86-7.88 (m, 1H, arom.), 9.22 (s, 1H, > NH)

B. 3-Octadecanoylindol-2-yl-propionic acid

70 mg (0.15 mmol) 3-Octadecanoylindol-2-yl-propionic acid methyl ester is saponified according to Example 28 B.
Yield: 42 mg (61%)
Melting point: 134-136°C
$C_{29}H_{45}NO_3$ (455.7)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.21-1.37 (m, 26H, $-(CH_2)_{13}-$), 1.44 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.78 (quint, 2H, -$\underline{CH_2}$-CH_2-CO-aryl, J = 7 Hz), 2.90 (t, 2H, $-CH_2-$, J = 6 Hz), 3.03 (t, 2H, $-CH_2$-CO-, J = 7 Hz), 3.44 (t, 2H, $-CH_2-$, J = 6 Hz), 7.21-7.28 (m, 2H, arom.), 7.37-7.39 (m, 1H, arom.), 7.86-7.88 (m, 1H, arom.)

Example 31

1-Methyl-3-octadecanoylindol-2-yl-propionic acid

The mixture of 46 mg (0.1 mmol) 3-Octadecanoylindol-2-yl-propionic acid methyl ester (see Example 30 A), 20 mg (0.11 mmol) p-toluenesulfonic acid methyl ester, 13 mg (0.04 mmol) tetrabutylammonium bromide, 5 ml ether, 2 ml CH_2Cl_2 and 60 mg (1.5 mmol) powdered NaOH is stirred 5 h at room temperature. Then the mixture is suctioned off and the filter cake washed twice with ether/CH_2Cl_2 (1:1). The filtrate is concentrated and the 1-Methyl-3-octadecanoylindol-2-yl-propionic acid methyl ester that develops is precipitated from methanol. This is then saponified according to Example 28 B.
Yield: 22 mg (47%)
Melting point: 106-108°C
$C_{23}H_{47}NO_3$ (469.7)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.17-1.38 (m, 26H, $-(CH_2)_{13}$), 1.43 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.79 (quint, 2H, $\underline{CH_2}$-CH_2-CO-aryl, J = 7 Hz), 2.83 (t, 2H, $-CH_2-$, J = 7 Hz), 3.05 (t, 2H, $-CH_2$-CO-, J = 7 Hz), 3.47 (t, 2H, $-CH_2-$, J = 7 Hz), 3.80 (s, 3H, > N-CH_3), 7.28-7.32 (m, 2H, arom.), 7.36-7.40 (m, 1H, arom.), 7.86-7.91 (m, 1H, arom.)

Example 32

3-(1-Octadecanoylaminooctadecyl)indole-2-carboxylic acid

A. 3-(1-Hydroxyiminooctadecyl)indole-2-carboxylic acid ethyl ester

The mixture of 2.28 g (5 mmol) 3-Octadecanoylindole-2-carboxylic acid ethyl ester (see Example 1 A), 850 mg hydroxylamine-hydrochloride, 40 ml absolute ethanol and 13 ml absolute pyridine is heated 2 h to boiling at reflux. After cooling it is diluted with water, acidified using diluted H_3PO_4 and extracted twice with ether/CH_2Cl_2 3:1. The organic phases are washed with water, dried over Na_2SO_4 and concentrated. The residue is mixed with petrol ether and allowed to stand for a short time. The substance that precipitates in this process is suctioned off; from the filtrate, the product is isolated using column chromatography (silica gel with petrol ether/ethyl acetate 1.9:1 and 2.7:3). After concentration of the product fractions, an oil remains that crystallizes after some time.
Yield: 0.78 g (33%)
Melting point: 71-74°C

$C_{29}H_{46}N_2O_3$ (470.7)
MS: m/z (rel. int.) = 471 (45%), 427 (100%), 215 (62%)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, -CH_3, J = 7 Hz), 1.08-1.35 (m, 28H, -$(CH_2)_{14}$-), 1.39 (t, 3H, -O-CH_2-$\underline{CH_3}$, J = 7 Hz), 1.44 (quint, 2H, -$\underline{CH_2}$, -CH_2-CNOH-, J = 8 Hz), 2.87 (t, 2H, -CH_2-CNOH-, J = 8 Hz), 4.40 (g, 2H, -O-$\underline{CH_2}$-CH_3, J = 7 Hz), 7.14-7.18 (m, 1H, arom.), 7.28-7.33 (m, 2H, arom.), 7.68 (d, 1H, arom., J = 8 Hz), 9.16 (s, 1H, > CNOH)

B. 3-(1-Octadecanoylaminooctadecyl)indole-2-carboxylic acid ethyl ester

235 mg (0.5 mmol) 3-(1-Hydroxyiminooctadecyl)indole-2-carboxylic acid ethyl ester and 1.7 g sodium acetate are dissolved in 30 ml glacial acetic acid. After addition of 1 g zinc dust, stirring is continued 45 min. at room temperature. The mixture is poured into 350 ml ice cold 2 M NaOH and extracted with ether. The organic phase is dried over Na_2SO_4 and concentrated. The residue is mixed with the solution of 86 mg (0.7 mmol) 4-dimethylaminopyridine and 1 ml absolute triethylamine in 5 ml $CHCl_3$ and immediately after that mixed with the solution of 182 mg (0.6 mmol) octadecanoic acid chloride in 5 ml $CHCl_3$. Stirring is continued for 15 min., then diluted hydrochloric acid is added and extraction is carried out twice with ether. The organic phase is washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The residue is chromatographed on silica gel with petrol ether/ethyl acetate 1.8.5[sic]:1.5 and 2.8:2 and the product is recrystallized from petrol ether.
Yield: 203 g (56%)
Melting point: 84-86°C
$C_{47}H_{82}N_2O_3$ (723.2)
MS: m/z (rel. int.) = 724 (10%), 695 (20%), 483 (9%), 412 (38%), 391 (90%), 284 (79%), 149 (100%), 113 (41%)
^{1}H-NMR: δ (ppm) = 0.88 (t, 6H, -CH_3 and -CH_3, J = 7 Hz), 1.08-1.39 (m, 58H, -$(CH_2)_{14}$- and –$(CH_2)_{15}$-), 1.46 (t, 3H, -O-CH_2-$\underline{CH_3}$, J = 7 Hz), 1.57-1.65 (m, 2H, -$\underline{CH_2}$-CH_2-CO-), 1.76-1.94 (m, 2H, -$\underline{CH_2}$-CH <), 2.17 (t, 2H, -CH_2-CO-, J = 8 Hz), 4.46 (g, 2H, -O-$\underline{CH_2}$-CH_3, J = 7 Hz), 5.73-5.79 (m, 1H, -CH_2-$\underline{CH}$ <), 7.15-7.19 (m, 1H, arom.), 7.32-7.37 (m, 2H, arom.), 7.65 (d, 1H, > CH-$\underline{NH}$-CO-, J = 9 Hz), 7.84 (d, 1H, arom., J = 8 Hz), 8.74 (s, 1H, 3 > NH)

C. 3-(1-Octadecanoylaminooctadecyl)indole-2-carboxylic acid

The mixture of 72 g (0.1 mmol) 3-(1-Octadecanoylminooctadecyl)indole-2-carboxylic acid ethyl ester and 15 ml ethanol and 5 ml 10% aqueous KOH solution is heated 30 min to boiling at reflux. Then the mixture is mixed with water, acidified using 10% hydrochloric acid and extracted with ether. The organic phases are washed with diluted hydrochloric acid, dried over Na_2SO_4 and concentrated. The product is precipitated from methanol.
Yield: 33 g (47%)
Melting point: 56-58°C
$C_{45}H_{78}N_2O_3$ (695.1)
^{1}H-NMR: δ (ppm) = 0.88 (t, 6H, -CH_3 and -CH_3, J = 7 Hz), 1.03-1.38 (m, 58H, -$(CH_2)_{14}$- and –$(CH_2)_{15}$-), 1.52-1.64 (m, 2H, -$\underline{CH_2}$-CH_2-CO-), 1.97-2.07 (m, 2H, -$\underline{CH_2}$-CH <), 2.20 (t, 2H, -CH_2-CO-, J = 8 Hz), 5.43-5.53 (m, 1H, -CH_2-$\underline{CH}$ <), 6.95 (broad, 1H, > CH-$\underline{NH}$-CO-) 7.15(t, 1H, arom., J = 8 Hz), 7.33 (t, 1H, arom., J = 8 Hz), 7.39 (d, 1H, arom., J = 8 Hz), 7.76 (d, 1H, arom., J = 8 Hz), 8.92 (s, 1H, > NH)

Example 33

3-[1-(3-Phenylpropionylamino)octadecyl]indole-2-carboxylic acid

A. 3-[1-(3-Phenylpropionylamino)octadecyl]indole-2-carboxylic acid ethyl ester

Preparation according to Example 32 B with 101 mg (0.6 mmol) 3-Phenylpropionic acid chloride instead of octadecanoic acid chloride. The column chromatography is carried out with petrol ether/ethyl acetate 1.7.5:2.5[sic] and 2.7:3. After removal of the eluent, the product remains as a waxy substance.
Yield: 153 g (52%)
$C_{38}H_{56}N_2O_3$ (588.9)
MS: m/z (rel. int.) = 589 (66%), 561 (100%), 412 (99%), 349 (53%), 150 (65%)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, -CH_3, J = 7 Hz), 1.00-1.37 (m, 30H, -$(CH_2)_{15}$-), 1.44 (t, 3H, -O-CH_2-$\underline{CH_3}$-, J = 7 Hz), 1.70-1.87 (m, 2H, -$\underline{CH_2}$-CH <), 2.40-2.55 (m, 2H, -CH_2-), 2.88-3.01 (m, 2H, -CH_2-), 4.41 (q, 2H, -O-$\underline{CH_2}$-CH_3, J = 7 Hz), 5.70-5.76 (m, 1H, -CH_2-$\underline{CH}$ <), 7.11-7.22 (m, 6H, arom.), 7.33-7.39 (m, 2H, arom.), 7.62 (d, 1H, > CH-$\underline{NH}$-CO-, J = 9 Hz), 7.82 (d, 1H, arom., J = 8 Hz), 8.75 (s, 1H, > NH)

B. 3-[1-(3-Phenylpropionylamino)octadecyl]indole-2-carboxylic acid

Preparation from 3-[1-(3-Phenylpropionylamino)octadecyl]indole-2-carboxylic acid ethyl ester according to Example 32 C. After removal of the eluent, the product remains as a waxy substance.
Yield: 41 g (73%)
$C_{36}H_{52}N_2O_3$ (560.8)

^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.00-1.37 (m, 30H, $-(CH_2)_{15}-$), 1.87-2.00 (m, 2H, $-\underline{CH_2}-CH$ <), 2.44-2.57 (m, 2H, $-CH_2-$), 2.87-2.98 (m, 2H, $-\underline{CH_2}-$), 5.45-5.51 (m, 1H, $-CH_2-\underline{CH}$ <), 6.84 (m, 1H, > CH-$\underline{NH}$-CO-), 7.08-7.15 (m, 6H, arom.), 7.34 (t, 1H, arom., J = 8 Hz), 7.40 (d, 1H, arom., J = 8 Hz), 7.67 (d, 1H, arom., J = 8 Hz), 8.89 (s, 1H, > NH)

Example 34

3-(1-Acetylaminooctadecyl)indole-2-carboxylic acid

A. 3-(1-Acetylaminooctadecyl)indole-2-carboxylic acid ethyl ester

Preparation according to Example 32 B with 47 mg (0.6 mmol) Acetyl chloride instead of octadecanoic acid chloride. In the column chromatography, elution carried out with petrol ether/ethyl acetate 1.73:3 and 2.1:1. The oil remaining after concentration of the product fractions crystallizes after some time.
Yield: 95 g (38%)
Melting point: 98-101°C
$C_{31}H_{50}N_2O_3$ (498.9)
MS: m/z (rel.Int.) = 499 (76%), 471 (90%), 440 (73%), 412 (93%), 259 (100%)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.09-1.41 (m, 30H, $-(CH_2)_{15}-$), 1.47 (t, 3H, $-O-CH_2-\underline{CH_3}-$, J = 7 Hz), 1.75-1.94 (m, 2H, $-\underline{CH_2}-CH$ <), 1.97 (s, 3H, $-CO-CH_3-$), 4.46 (q, 2H, $-O-\underline{CH_2}-CH_3$, J = 7 Hz), 5.71-5.77 (m, 1H, $-CH_2-\underline{CH}$ <), 7.16-7.20 (m, 1H, arom.), 7.33-7.38 (m, 2H, arom.), 7.70 (d, 1H > CH-$\underline{NH}$-CO-, J = 9 Hz), 7.85 (d, 1H, arom., J = 9 Hz), 8.76 (s, 1H, > NH)

B. 3-(1-Acetylaminooctadecyl)indole-2-carboxylic acid

The mixture of 50 mg. (0.1 mmol) 3-(1-Acetylaminooctadecyl)indole-2-carboxylic acid ethyl ester, 15 mg ethanol and 5 ml 10% aqueous KOH solution is heated to boiling 30 min at reflux. Then the mixture is mixed with 2.5% Na2CO3 solution and washed with ether. The aqueous phase is carefully acidified with diluted hydrochloric acid and extracted with ether. The organic phase is dried over Na2SO4 and concentrated. The product remains as oil.
Yield: 22 g (73%)
Melting point: from 65°C
$C_{29}H_{46}N_2O_3$ (470.7)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.08-1.38 (m, 30H, $-(CH_2)_{15}-$), 1.93-2.05 (m, 2H, $-\underline{CH_2}-CH$ <), 2.02 (s, 3H, $-CO-CH_3$), 5.54-5.60 (m, 1H, $-CH_2-\underline{CH}$ <), 7.15 (t, 1H, arom., J = 8 Hz), 7.33 (t, 1H, arom., J = 8 Hz), 7.40 (d, 1H, arom., J = 8 Hz), 7.78 (d, 1H, arom., J = 8 Hz), 8.96 (s, 1H, > NH)

Example 35

1-Methyl-3-(1-octadecanoylaminooctadecyl)indole-2-carboxylic acid

A. 1-Methyl-3-(1-octadecanoylaminooctadecyl)indole-2-carboxylic acid ethyl ester

The mixture of 108 mg (0.15 mmol) 3-(1-Octadecanoylaminooctadecyl)indole-2-carboxylic acid ethyl ester (see Example 32 B), 32 mg (0.17 mmol) p-Toluenesulfonic acid methyl ester, 13 mg (0.04 mmol) Tetrabutylammonium bromide, 5 ml CH_2Cl_2 and 16 mg (0.4 mmol) powdered NaOH is stirred 7 h at room temperature. Then the mixture is mixed with water and extracted with ether. The ether phase is washed twice with saturated Na_2CO_3 solution, dried over Na_2SO_4 and concentrated. The product is precipitated from methanol.
Yield: 82 g (74%)
Melting point: 78-80°C
$C_{48}H_{84}N_2O_3$ (737.2)
^{1}H-NMR: δ (ppm) = 0.88 (t, 6H, $-CH_3$ and $-CH_3$, J = 7 Hz), 1.04-1.41 (m, 58H, $-(CH_2)_{14}-$ and $-(CH_2)_{15}-$), 1.49 (t, 3H, $-O-CH_2-\underline{CH_2}-$, J = 7 Hz), 1.53-1.67 (m, 2H, $-\underline{CH_2}-CH_2-CO-$), 1.75-1.97 (m, 2H, $-\underline{CH_2}-CH$ <), 2.14 (t, 2H, $-CH_2-CO-$, J = 8 Hz), 3.97 (s, 3H, > $N-CH_3$), 4.48 (q, 1H, $-O-\underline{CH_2}-CH_3$, J = 7 Hz) , 5.77-5.83 (m, 1H, $-CH_2-\underline{CH}$ <), 7.15-7.19 (m, 2H > CH-$\underline{NH}$-CO-, and arom.), 7.33-7.39 (m, 2H, arom.), 7.85 (d, 1H, arom., J = 8 Hz)

B. 1-Methyl-3-(1-octadecanoylaminooctadecyl)indole-2-carboxylic acid

Preparation from 1-Methyl-3-(1-octadecanoylaminooctadecyl)indole-2-carboxylic acid ethyl ester according to Example 32 C. After concentration of the ether phase, the product remains as a solid material.
Yield: 32 g (45%)
Melting point: 110-113°C
$C_{46}H_{80}N_2O_3$ (709.2)
^{1}H-NMR: δ (ppm) = 0.88 (t, 6H, $-CH_3$ and $-CH_3$, J = 7 Hz), 1.07-1.34 (m, 58H, $-(CH_2)_{14}-$ and $-(CH_2)_{15}-$), 1.46-1.66 (m, 2H, $-\underline{CH_2}-CH_2-CO-$), 2.07-2.23 (m, 4H, $-\underline{CH_2}-CH$ < and $-\underline{CH_2}-CO-$), 3.92 (s, 3H, > $N-CH_3-$), 5.08-5.14 (m, 1H, $-\underline{CH_2}-CH$ <), 6.33 (d, 1H >

CH-<u>NH</u>-CO-, J = 6 Hz), 7.13 (t, 1H, arom., J = 8 Hz), 7.33 (t, 1H, arom., J = 8 Hz), 7.39 (d, 1H, arom., J = 8 Hz), 7.66 (d, 1H, arom., J = 8 Hz)

Example 36

1-Methyl-3-[1-(3-phenylpropionylamino)octadecyl]indole-2-carboxylic acid

A. 1-Methyl-3-[1-(3-phenylpropionylamino)octadecyl]indole-2-carboxylic acid ethyl ester

Preparation from 3-[1-(3-Phenylpropionylamino)octadecyl]indole-2-carboxylic acid ethyl ester (see Example 33 A) according to Example 35 A. However, the product is purified using column chromatography (silica gel, petrol ether/ethyl acetate 1.9:1 and 2.8:2). After removal of the eluent, the product remains as a waxy substance.
Yield: 71 g (79%)
$C_{39}H_{58}N_2O_3$ (602.9)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.05-1.37 (m, 30H, $-(CH_2)_{15}-$), 1.46 (t, 3H, $-O-CH_2-\underline{CH_3}$, J = 7 Hz), 1.69-1.89 (m, 2H, $-\underline{CH_2}-CO$ <), 2.38-2.50 (m, 2H, $-CH_2-$), 2.86-3.00 (m, 2H, $-CH_2-$), 3.97 (s, 3H, $-CO-CH_3-$), 4.43 (q, 2H, $-O-\underline{CH_2}-CH_3$, J = 7 Hz), 5.75-5.81 (m, 1H, $-CH_2-\underline{CH}$ <), 7.08 (d, 1H > CH-<u>NH</u>-CO-, J = 9.5 Hz), 7.10-7.18 (m, 6H, arom.), 7.29-7.40 (m, 2H, arom.), 7.79 (d, 1H, arom., J = 8 Hz)

B. 1-Methyl-3-[1-(3-phenylpropionylamino)octadecyl]indole-2-carboxylic acid

Preparation according to Example 32 C. After concentration of the ether phase, the product remains as a waxy substance.
Yield: 42 g (73%)
$C_{37}H_{54}N_2O_3$ (574.8)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.03-1.37 (m, 30H, $-(CH_2)_{15}-$), 1.89-2.08 (m, 2H, $-O-CH_2-CH$ <), 2.43-2.55 (m, 2H, $-CH_2-$), 2.88 (t, 2H, $-CH_2-$, J = 7 Hz), 3.92 (s, 3H, $-CO-CH_3-$), 5.04-5.10 (m, 1H, $-CH_2-\underline{CH}$ <), 6.26 (d, 1H > CH-<u>NH</u>-CO-, J = 6 Hz), 7.04-7.14 (m, 6H, arom.), 7.34 (t, 1H, arom., J = 8 Hz), 7.39 (d, 1H, arom., J = 8 Hz), 7.51 (d, 1H, arom., J = 8 Hz)

Example 37

1-Methyl-3-(1-acetylaminooctadecyl)indole-2-carboxylic acid

A. 1-Methyl-3-(1-acetylaminooctadecyl)indole-2-carboxylic acid ethyl ester

Preparation from 3-(1-Acetylaminooctadecyl)indole-2-carboxylic acid ethyl ester (see Example 34 A) according to Example 35 A. However, the product is purified using column chromatography (silica gel, petrol ether/ethyl acetate 1.8:2 and 2.9:1). After removal of the eluent, the product remains as a waxy substance.
Yield: 70 mg (91%)
$C_{32}H_{52}N_2O_3$ (512.8)
^{1}H-NMR: δ (ppm) = 0.88 (t, 6H, $-CH_3$, J = 7 Hz), 1.03-1.42 (m, 30H, $-(CH_2)_{15}-$), 1.49 (t, 3H, $-O-CH_2-\underline{CH_3}$, J = 7 Hz), 1.74-1.97 (m, 2H, $-CH_2-CH$ <), 1.95 (s, 3H, $-CO-CH_3-$), 3.97 (s, 3H, > $N-CH_3$), 4.49 (q, 2H, $-O-\underline{CH_2}-CH_3$, J = 7 Hz), 5.76-5.82 (m, 1H, $-CH_2-\underline{CH}$ <), 7.15-7.20 (m, 2H, > CH-<u>NH</u>-CO- and arom.), 7.33-7.40 (m, 2H, arom.), 7.85 (d, 1H, arom., J = 8 Hz)

B. 1-Methyl-3-(1-acetylaminooctadecyl)indole-2-carboxylic acid

Preparation according to Example 32 C. After concentration of the ether phase, the product remains as a solid material.
Yield: 33 mg (68%)
Melting point: 134-137°C
$C_{30}H_{48}N_2O_3$ (484.7)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.05-1.36 (m, 30H, $-(CH_2)_{15}-$), 1.99 (t, 3H, $-O-CH_3$), 2.04-2.19 (m, 2H, $-\underline{CH_2}-CH$ <), 3.92 (s, 3H, $-CO-CH_3-$), 5.10-5.16 (m, 1H, $-CH_2-\underline{CH}$ <), 6.41 (d, 1H, > CH-<u>NH</u>-CO-, J = 6 Hz), 7.14 (t, 1H, arom., J = 8 Hz), 7.35 (t, 1H, arom., J = 8 Hz), 7.40 (d, 1H, arom., J = 8 Hz), 7.68 14 (d, 1H, arom., J = 8 Hz)

Example 38

1-Methyl-3-octadecylindole-2-carboxylic acid

The mixture of 94 mg (0.2 mmol) 1-Methyl-3-octadecanoylindole-2-carboxylic acid ethyl ester (see Example 2 A), 2 ml absolute THF, 3 ml absolute methyl acetate, 40 mg $NaBH_4$ and 0.2 ml BF_3 Ethyl ester complex is stirred 1 h at room temperature. After addition of 2 ml methanol (50%), stirring continues 15 min more, then the mixture is diluted with water and extracted twice with ether. The organic phase is concentrated and the 1-Methyl-3-octadecylindole-2-carboxylic acid ethyl ester obtained is

saponified according to Example 1 B, whereby ether is used to extract the carboxylic acid ether formed instead of CH_2Cl_2. The product is precipitated from methanol.
Yield: 24 mg (26%)
Melting point: 87-90°C
$C_{30}H_{49}N_2O_3$ (455.7)
^{1}H-NMR: δ (ppm) = 0.88 (t, 3H, $-CH_3$, J = 7 Hz), 1.11-1.39 (m, 28H, $-(CH_2)_{14}-$), 1.41 (quint, 2H, $-CH_2-$, J = 7 Hz), 1.68 (quint, 2H, $-\underline{CH_2}-CH_2$-Indolyl, J = 7 Hz), 3.15 (t, 2H, $-\underline{CH_2}$-CO-Indolyl, J = 7 Hz), 4.05 (s, 3H, > $N-CH_3$), 7.13-7.17 (m, 1H, arom.), 7.36-7.41 (m, 2H, arom.), 7.70 (d, 1H, arom., J = 8 Hz)

Example 39

The effectiveness of the compounds according to the invention can be determined by the inhibition of phospholipase A_2. The test method used was already described (see Lehr, Matthias: In-vitro assay for the evaluation of phospholipaseA_2 inhibitors using bovine platelets and HPLC with UV detection. Phar. Pharacol. Lett. 1992, 2, 176-179).

The test substances are usually dissolved in DMSO, with heating if necessary. For substances that did not dissolve in this solvent, a mixture of DMSO/0.05 M ethanolic NaOH (1:1) was used as the solvent. In the latter case, as a deviation from the specification cited above, the thrombocyte suspension was not pipetted into the test substance solution, but in contrast the test substance solution was pipetted into the thrombocyte suspension.

The results obtained in the testing of compounds according to the invention are listed in the following Table 5. With the test system used, the inhibition value indicated in Table 6 was obtained for the known PLA_2 inhibitor, N-(S)-Hexadecyl-2-pyrrolidine carboxamide (McGregor et al., US Patent 4792555).

Table 5

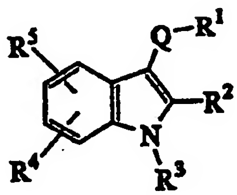
Compound from Example No.	% Inhibition of PLA_2 at 10 μM
2	61
5	62
6	63
9	82
10	79
11	76
12	75

Table 6

Compound	% Inhibition of PLA_2 at 10 μM
N-(S)-Hexadecyl-2-pyrrolidinecarboxamide	42

Patent Claims

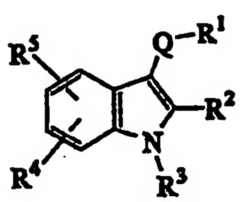
1. Substituted indole compounds of the general formula:



wherein
R^1 stands for X, aryl or –X-Aryl, whereby X is a C_1-C_{19}-alkyl and/or C_2-C_{19}-alkenyl or alkinyl group that may be interrupted by an oxygen heteroatom, and aryl indicates an aryl group or an aryl group substituted with the radicals R^6 and R^7;
R^2 stands for –COOH, -Y-COOH, -Tz or –Y-Tz, whereby Y indicates a C_1-C_8-alkyl and/or C_2-C_8-alkenyl group that may be interrupted by an oxygen heteroatom and Tz indicates 1H- or 2H-tetrazol-5-yl;
R^3 stands for a hydrogen atom; for a C_1-C_{20}-alkyl and/or C_2-C_{20}-alkenyl or alkinyl group that may be interrupted by an oxygen heteroatom; for an aryl group or an aryl group substituted with the radicals R^8 and R^9; for –Z-aryl, whereby Z indicates a C_1-C_{20}-alkyl and/or C_2-C_{20}-alkenyl or alkinyl group that may be interrupted by an oxygen heteroatom and aryl indicates an aryl group or an aryl group substituted with the radicals R^8 and R^9; for –Z-OR^{16}, -Z-SR^{16}or –Z-NHR^{16}, whereby Z indicates a C_2-C_{20} alkyl and/or C_2-C_{20}-alkenyl or alkinyl group that may be interrupted by an oxygen heteroatom;
Q stands for CO, CH_2 and $CHNHCOR^{10}$, whereby R^{10} stands for W, aryl or –W-aryl and W can be a C_1-C_{19}-alkyl and/or C_2-C_{19}-alkenyl or alkinyl group that may be interrupted by an oxygen heteroatom and aryl indicates an aryl group or an aryl group substituted with the radicals R^{11} and R^{12}; R^4, R^5, R^6, R^7, R^8, R^9, R^{11} and R^{12} are selected independently of each other from among:
1) Hydrogen;
2) C_1-C_{20}-alkyl group that may be interrupted by an oxygen heteroatom;
3) C_2-C_{20}-alkenyl group that may be interrupted by an oxygen heteroatom;
4) C_2-C_{20}-alkinyl group that may be interrupted by an oxygen heteroatom;
5) Halogen;
6) $-CF_3$;
7) –CN;
8) $-NO_2$;
9) $-OR^{13}$;
10) $-SR^{13}$;
11) $-COOR^{13}$;
12) $-COR^{14}$;
13) $-COCH_2OH$;
14) $-NHCOR^{13}$;
15) $-NR^{13}R^{13}$;
16) $-NHSO_2R^{15}$;
17) $-SOR^{13}$;
18) $-SO_2R^{13}$;
19) $-CONR^{13}R^{13}$;
20) $-SO_2NR^{13}R^{13}$;
21) $-OOCR^{14}$;
22) $-OOCNR^{13}R^{13}$;
23) $-OOCOR^{13}$;
24) $-(CH_2)_rOR^{16}$;
25) $-(CH_2)_rSR^{16}$;
26) $-(CH_2)_rNHR^{16}$;
27) $-(CH_2)_sR^{17}$;
28) Perhalo-C_1-C_6-alkenyl;
R^{13} indicates, independently of each other, hydrogen, a C_1-C_{20}-alkyl and/or C_2-C_{19}-alkenyl or alkinyl group or $-(CH_2)_tR^{17}$;
R^{14} indicates, independently of each other, R^{13}, $-CF_3$, $-(CH)_2)_uCOOH$ or $-(CH_2)_uCOOR^{19}$;
R^{15} indicates, independently of each other, R^{13} or CF_3;
R^{16} indicates, independently of each other, hydrogen or $-COR^{19}$;
R^{17} indicates, independently of each other, aryl, substituted with one or two R^{18} groups;

R^{18} indicates, independently of each other, hydrogen, halogen, C_1-C_{12}-alkyl, C_1-C_{12}-alkoxy, C_1-C_{12}-alkylthio, C_1-C_{12}-alkylsulfonyl, C_1-C_{12}-alkylcarbonyl, -CF_3, -CN or NO_2;
R^{19} indicates, independently of each other, C_1-C_6-alkyl, benzyl or phenyl;
r is 1 to 20;
s and t, independently of each other, are 0 to 12;
u is 0 to 4
and their pharmaceutically compatible salts and esters for use in pharmaceuticals.

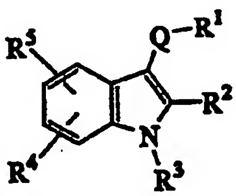
2. Compounds according to Claim 1of the general formula:



wherein
R^1 stands for X, aryl or –X-Aryl, whereby X is a C_1-C_{19}-alkyl and/or C_2-C_{19}-alkenyl group , and aryl indicates an aryl group or an aryl group substituted with the radicals R^6 and R^7;
R^2 stands for –COOH, -Y-COOH, -Tz or –Y-Tz, whereby Y indicates a C_1-C_8-alkyl and/or C_2-C_8-alkenyl group and Tz indicates 1H- or 2H-tetrazol-5-yl;
R^3 stands for a hydrogen atom; for a C_1-C_{20}-alkyl and/or C_2-C_{20}-alkenyl group; for an aryl group or an aryl group substituted with the radicals R^8 and R^9; for –Z-aryl, whereby Z indicates a C_1-C_{20}-alkyl and/or C_2-C_{20}-alkenyl group and aryl indicates an alyl[sic] group or an aryl group substituted with the radicals R^8 and R^9; for –Z-OR^{16}, -Z-SR^{16}or –Z-NHR^{16}, whereby Z indicates a C_2-C_{20} alkyl and/or C_2-C_{20}-alkenyl group;
Q stands for CO, CH_2 and $CHNHCOR^{10}$, whereby R^{10} stands for W, aryl or –W-aryl and W can be a C_1-C_{19}-alkyl and/or C_2-C_{19}-alkenyl group and aryl indicates an aryl group or an aryl group substituted with the radicals R^{11} and R^{12}; R^4, R^5, R^6, R^7, R^8, R^9, R^{11} and R^{12} are selected independently of each other from among:
1) Hydrogen;
2) C_1-C_{20}-alkyl group;
3) C_2-C_{20}-alkenyl group;
4) C_2-C_{20}-alkinyl group;
5) Halogen;
6) –CF_3;
7) –CN;
8) –NO_2;
9) –OR^{13};
10) –SR^{13};
11) –$COOR^{13}$;
12) –COR^{14};
13) –$COCH_2OH$;
14) –$NHCOR^{13}$;
15) –$NR^{13}R^{13}$;
16) –$NHSO_2R^{15}$;
17) –SOR^{13};
18) –SO_2R^{13};
19) –$CONR^{13}R^{13}$;
20) –$SO_2NR^{13}R^{13}$;
21) –$OOCR^{14}$;
22) –$OOCNR^{13}R^{13}$;
23) –$OOCOR^{13}$;
24) –$(CH_2)_rOR^{16}$;
25) –$(CH_2)_rSR^{16}$;
26) –$(CH_2)_rNHR^{16}$;
27) –$(CH_2)_sR^{17}$;
28) Perhalo-C_1-C_6-alkenyl;
R^{13} indicates, independently of each other, hydrogen, a C_1-C_{20}-alkyl and/or C_2-C_{19}-alkenyl group
or –$(CH_2)_tR^{17}$;
R^{14} indicates, independently of each other, hydrogen, R^{13}, -CF_3, -$(CH)_2)_uCOOH$ or –$(CH_2)_uCOOR^{19}$;

R^{15} indicates, independently of each other, R^{13} or CF_3;
R^{16} indicates, independently of each other, hydrogen or $-COR^{19}$;
R^{17} indicates, independently of each other, aryl, substituted with one or two R^{18} groups;
R^{18} indicates, independently of each other, hydrogen, halogen, C_1-C_{12}-alkyl, C_1-C_{12}-alkoxy, C_1-C_{12}-alkylthio, C_1-C_{12}-alkylsulfonyl, C_1-C_{12}-alkylcarbonyl, $-CF_3$, -CN or NO_2;
R^{19} indicates, independently of each other, C_1-C_6-alkyl, benzyl or phenyl;
r is 1 to 20;
s and t, independently of each other, are 0 to 12;
u is 0 to 4;
and their pharmaceutically compatible salts and esters for use in pharmaceuticals.

3. Compounds according to Claim 1 of the general formula:

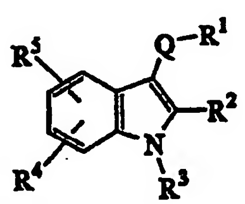


wherein
R^1 stands for X, aryl or –X-Aryl, whereby X is a C_1-C_{19}-alkyl and/or C_2-C_{19}-alkenyl group , and aryl indicates an aryl group or an aryl group substituted with the radicals R^6 and R^7;
R^2 stands for –COOH, -Y-COOH, -Tz or –Y-Tz, whereby Y indicates a C_1-C_8-alkyl group;
R^3 stands for a hydrogen atom; for a C_1-C_{20}-alkyl and/or C_2-C_{20}-alkenyl group; for an aryl group or an aryl group substituted with the radicals R^8 and R^9; for –Z-aryl, whereby Z indicates a C_1-C_{20}-alkyl and/or C_2-C_{20}-alkenyl group and aryl indicates an aryl group or an aryl group substituted with the radicals R^8 and R^9; for $-Z-OR^{16}$, $-Z-SR^{16}$or $-Z-NHR^{16}$, whereby Z indicates a C_2-C_{20} alkyl and/or C_2-C_{20}-alkenyl group;
Q stands for CO, CH_2 and $CHNHCOR^{10}$, whereby R^{10} stands for W, aryl or –W-aryl and W can be a C_1-C_{19}-alkyl and/or C_2-C_{19}-alkenyl group and aryl indicates an aryl group or an aryl group substituted with the radicals R^{11} and R^{12}; R^4, R^5, R^6, R^7, R^8, R^9, R^{11} and R^{12} are selected independently of each other from among:
1) Hydrogen;
2) C_1-C_{20}-alkyl group;
3) C_2-C_{20}-alkenyl group;
4) Halogen;
5) $-CF_3$;
6) –CN;
7) $-NO_2$;
8) $-OR^{13}$;
9) $-SR^{13}$;
10) $-COOR^{13}$;
11) $-COR^{14}$;
12) $-COCH_2OH$;
13) $-NHCOR^{13}$;
14) $-NR^{13}R^{13}$;
15) $-NHSO_2R^{15}$;
16) $-SOR^{13}$;
17) $-SO_2R^{13}$;
18) $-CONR^{13}R^{13}$;
19) $-SO_2NR^{13}R^{13}$;
20) $-OOCR^{14}$;
21) $-OOCNR^{13}R^{13}$;
22) $-OOCOR^{13}$;
23) $-(CH_2)_rOR^{16}$;
24) $-(CH_2)_sR^{17}$;
25) Perhalo-C_1-C_6-alkenyl;
R^{13} indicates, independently of each other, hydrogen, a C_1-C_{20}-alkyl and/or C_2-C_{19}-alkenyl group or $-(CH_2)_tR^{17}$;
R^{14} indicates, independently of each other, R^{13}, $-CF_3$, $-(CH)_2)_uCOOH$ or $-(CH_2)_uCOOR^{19}$;
R^{15} indicates, independently of each other, R^{13} or CF_3;
R^{16} indicates, independently of each other, hydrogen or $-COR^{19}$;

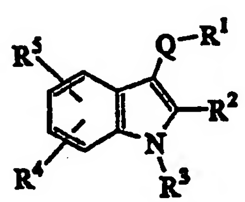
R^{17} indicates, independently of each other, aryl, substituted with one or two R^{18} groups;
R^{18} indicates, independently of each other, hydrogen, halogen, C_1-C_{12}-alkyl, C_1-C_{12}-alkoxy, C_1-C_{12}-alkylthio, C_1-C_{12}-alkylsulfonyl, C_1-C_{12}-alkylcarbonyl, -CF_3, -CN or NO_2;
R^{19} indicates, independently of each other, C_1-C_6-alkyl, benzyl or phenyl;
r is 1 to 20;
s and t, independently of each other, are 0 to 12;
u is 0 to 4;
and their pharmaceutically compatible salts and esters for use in pharmaceuticals.

4. Compounds according to Claim 1, namely:
1-Methyl-3-octanoylindole-2-carboxylic acid
1-Methyl-3-decanoylindole-2-carboxylic acid
1-Methyl-3-dodecanoylindole-2-carboxylic acid
1-Methyl-3-tetradecanoylindole-2-carboxylic acid
1-Methyl-3-octadecanoylindole-2-carboxylic acid
3-(2-Dodecyloxybenzoyl)-1-methylindole-2-carboxylic acid
3-(3-Dodecyloxybenzoyl)-1-methylindole-2-carboxylic acid
3-(4-Dodecyloxybenzoyl)-1-methylindole-2-carboxylic acid
1-Hexyl-3-octadecaoylindole-2-carboxylic acid.

5. Method for producing substituted indole compounds according to Claim 1, characterized in that
A) into a compound of the general formula



in which R^3 stands for a hydrogen atom, and in which R^1, R^2, R^4, R^5 and Q correspond to the meanings indicated in Claim 1, a radical R^3 is introduced, possibly in a multi-level reaction, with a meaning that corresponds to those indicated in Claim 1 for R^3. If necessary, this reaction can also be followed by ester cleavage,
B) into a compound of the general formula



in which Q-R^1 stands for a hydrogen atom, and in which R^2, R^3, R^4, R^5 correspond to the meanings indicated in Claim 1, a radical Q-R^1 is introduced, possibly in a multi-level reaction, with a meaning that corresponds to those indicated in Claim 1 for Q-R^1. If necessary, this reaction can also be followed by ester cleavage.

6. Pharmaceutical preparation, containing at least one compound according to one of Claims 1 to 4, possibly with the usual pharmaceutically compatible auxiliary materials and/or additives.

7. Pharmaceutical preparation according to Claim 6 for use as an inhibitor of phospholipase A_2.

8. Use of at least one compound according to one of Claims 1 to 4 for producing a pharmaceutical preparation for prevention and for treatment of diseases that are caused or partially caused by increased activity of phospholipase A_2, e.g. inflammation, allergies, asthma, psoriasis and endotoxic shock.

9. Method for producing the pharmaceutical preparation according to Claim 8, characterized in that at least one compound according to one of Claims 1 to 4 is prepared in a form suitable for administration, possibly with the use of the usual pharmaceutical carriers and/or additives.